35. 5,336,506, Aug. 9, 1994, Targeting of therapeutic agents using polysaccharides; Lee Josephson, et al., 424/488, 646; **435/178**; 514/2, 21, 54, 169, 179; 536/55.1 [IMAGE AVAILABLE]

US PAT NO: 5,336,506 [IMAGE AVAILABLE] L9: 35 of 181

ABSTRACT:
The invention relates to a method for the targeting of a therapeutic agent to a specific population of cells, wherein a complex is formed between the therapeutic agent and a polysaccharide capable of interacting with a cell receptor, and wherein the resulting complex is internalized into the cell by receptor mediated endocytosis (RME). In one embodiment of the invention, a complex of a therapeutic agent containing iron and the polysaccharide arabinogalactan may be formed and used to deliver iron specifically to hepatocytes by RME.

154. 4,939,240, Jul. 3, 1990, Monoclonal antibodies to human breast carcinoma cells and their use in diagnosis and therapy; Tsann M. Chu, et al., 530/388.85; 424/9, 156.1; **435/7.23**, **70.21**, **188**, **240.27**; 530/391.3, 391.7, 808, 809; 935/104, 107 [IMAGE AVAILABLE]

US PAT NO: 4,939,240 [IMAGE AVAILABLE] L9: 154 of 181

ABSTRACT:
Monoclonal antibodies to adenocarcinoma cells, and, in particular, breast carcinoma cells, are produced by a hybridoma formed by fusing mouse lymphocytes and mouse myeloma cells. The monoclonal antibodies are capable of shrinking solid tumors associated with human breast. The monoclonal antibodies identify an antigen associated with carcinomas of ductal lineage. The monoclonal antibodies, specifically, F36/22 monoclonal antibodies, can be used diagnostically and therapeutically.

=> d his

(FILE 'USPAT' ENTERED AT 12:41:23 ON 17 APR 95)

L1	2373	S TRANSFORMATION AND ANTIBODY
L2	69060	S TARGET OR GENE(W)THERAPY
L3	812	S L1 AND L2
L4	666	S L3 AND DNA
L5	246	S L4 AND CONJUGATE
L6	0	S 435/CLS
L7	29583	S 435/CLAS
L8	135	S 514/44/CCLS
L9	181	S L5 AND (L7 OR L8)

Set	Items	Description
S1	9384	ANTIBODY (2N) DNA
S2	11764	GENE(W)THERAPY
S3	59	S1 AND S2
S4	58	RD (unique items)
S5	912738	COMPLEX OR CONJUGATE
S6	1302	S1 AND S5
S7	67	S6 AND TARGET?
S8	54	RD (unique items)
S9	1246	PROTAMINE AND DNA
S10	192	S9 AND S5
S11	7	S10 AND S1
S12	4	RD (unique items)
S13	194	PROTAMINE(W)GENE
S14	106	S13 AND SEQUENCE
S15	61	RD (unique items)
S16	1709	PSEUDOMONAS(W)EXOTOXIN
S17	520	DOMAIN(W)III
S18	71	S16 AND S17
S19	31	RD (unique items)

?

4/9/7 (Item 5 from file: 73)
DIALOG(R)File 73:EMBASE

8472505 EMBASE No: 92148372
Engineered antibodies and antibody fragments for human disease management
Better M.; Theofan G.
USA
J. CLIN. IMMUNOASSAY (USA) , 1992, 15/1 (17-24) CODEN: JCLIE ISSN: 0736-4393
LANGUAGES: English SUMMARY LANGUAGES: English
SUBFILES: 022; 026

EMTAGS:
Genetic engineering 0108; Therapy 0160; Heredity 0137; Short survey 0002
MEDICAL DESCRIPTORS:
*genetic engineering; *antibody; **gene* *therapy*
gene technology; gene expression; chimera; antibody affinity; binding kinetics; *dna* transcription; immunogenicity; *antibody* production; recombinant *dna* technology; short survey

4/9/30 (Item 22 from file: 357)
DIALOG(R)File 357:Derwent Biotechnology Abs

166052 DBA Accession No.: 94-08603
Delivery of plasmid DNA to glial cells using pH-sensitive immunoliposomes - immunoliposome production containing beta-galactosidase- and glioma-specific monoclonal *antibody* for plasmid *DNA* delivery to C6 glioma cell culture; potential tumor *gene* *therapy*
AUTHOR: Holmberg E G; Reuer Q R; Geisert E E; Owens J L
CORPORATE AFFILIATE: Univ.Alaska-Anchorage
CORPORATE SOURCE: Department of Chemistry/Physics, University of Alaska-Anchorage, Anchorage, Alaska 99508, USA.
JOURNAL: Biochem.Biophys.Res.Commun. (201, 2, 888-93) 1994
CODEN: BBRCA9
LANGUAGE: English
ABSTRACT: Immunoliposomes were constructed with monoclonal antibodies 5-113 and 13-21 which are specific to glial cells and contain a gene expressing beta-galactosidase (EC-3.2.1.23). The liposomes were constructed by a previously described method, in the final step, plasmid DNA was added and the entire mixture was dialyzed for 48 hr at 4 deg. The liposomes were then sized 4 times through a 0.4 um Nucleopore membrane and they were then separated from free plasmid *DNA* and unconjugated *antibody* on a BioGel column. Liposomes were diluted to 1 mg/ml total lipid. Plasmid *DNA* and *antibody* concentrations were 0.025 mg/ml and 0.25 mg/ml, respectively, in the standard 1 mg/ml total lipid immunoliposome solution. Cultured C6 glioma cells were transfected using the immunoliposomes. There was a 3-fold increase in transfection by the glial-specific immunoliposomes (gliasomes) over control liposomes. Gliasomes were exposed to NIH3T3 cells and showed no enhanced transfection over control liposomes. These liposomes have the potential to carry drugs or genes to target sites in vitro or in vivo for the treatment of disease. (15 ref)
E.C. NUMBERS: 3.2.1.23
DESCRIPTORS: immunoliposome prep., beta-galactosidase-, glioma-specific

monoclonal *antibody*, appl. plasmid *DNA* delivery to C6 glioma cell culture, pot. tumor *gene* *therapy* liposome mammal animal enzyme EC-3.2.1.23 vector tumor (Vol.13, No.15)
SECTION: PHARMACEUTICALS-Clinical Genetic Techniques; GENETIC ENGINEERING AND FERMENTATION-Nucleic Acid Technology (D7,A1)

4/9/35 (Item 27 from file: 357)
DIALOG(R)File 357:Derwent Biotechnology Abs

163073 DBA Accession No.: 94-05624 PATENT
Intermedin receptor fusion protein production by plasmid pBD-11D or plasmid pE-MC-2 expression in Bacillus sp., Escherichia sp. or Salmonella sp., yeast, protozoon, fungus, insect, plant or mammal cell culture - monoclonal *antibody* and *DNA* sequence; application in e.g. melanoma, skin cancer, epilepsy and nerve damage *gene* *therapy*
PATENT ASSIGNEE: Wikberg J 1994
PATENT NUMBER: WO 9404674 PATENT DATE: 940303 WPI ACCESSION NO.: 94-083193 (9410)
PRIORITY APPLIC. NO.: DK 93528 APPLIC. DATE: 930505
NATIONAL APPLIC. NO.: WO 93DK273 APPLIC. DATE: 930820
LANGUAGE: English
ABSTRACT: The following are claimed: (1) a DNA fragment (DF) (I) of specified DNA sequence which encodes an intermedin receptor; (2) a DF encoding a protein; (3) a modified DF where at least 1 nucleotide has been substituted, added, inserted, deleted and/or rearranged; (4) a fusion DF, encoding a fusion protein, comprising the above, where the 2nd DF encodes diphtheria toxin, a Staphylococcus protein, a ricin toxin, a Pseudomonas endotoxin, abrin, and fungal ribosome-inactivation protein; (5) a protein which is an intermedin receptor which binds to an antibody, preferably a monoclonal antibody; (6) a fusion protein, encoded by a DF, fused to a 2nd fusion protein selected from an intermedin receptor, and an ACTH receptor, or their analogs and subsequences; (7) replicable expression vector plasmid pBD-11D (DSM 7214) and/or plasmid pE-MC-2 (DSM 8440) expressed in a host cell, organism or cell line for expression and production of (5); and (8) a stable cell line which produces a protein. The host cell is a bacterium, preferably Bacillus sp., Escherichia sp. or Salmonella sp., a yeast, a protozoon or a fungus, insect, plant or mammal cell. (134pp)
DESCRIPTORS: intermedin receptor fusion protein prep., plasmid pBD-11D, plasmid pE-MC-2 expression in Bacillus sp., Escherichia sp., Salmonella sp., yeast, protozoon, fungus, insect, plant, mammal cell culture, monoclonal *antibody*, *DNA* probe, *DNA* primer, DNA sequence, appl. e.g. melanoma, skin tumor, epilepsy, nerve damage diagnosis, therapy, *gene* *therapy* chimeric toxin polymerase chain reaction arthropod gene transmission cloning protein sequence animal vector bacterium (Vol.13, No.10)
SECTION: PHARMACEUTICALS-Peptides and Proteins; PHARMACEUTICALS-Clinical Genetic Techniques; PHARMACEUTICALS-Antibodies; GENETIC ENGINEERING AND FERMENTATION-Nucleic Acid Technology; CELL CULTURE-Animal Cell Culture (D3,D7,D6,A1,J1)

4/9/43 (Item 35 from file: 357)
DIALOG(R)File 357:Derwent Biotechnology Abs

148889 DBA Accession No.: 93-06941 PATENT
New complex for transporting gene into higher eukaryote cell - adeno virus vector, polylysine and antibody conjugate for transfection in e.g. *gene* *therapy* or antisense RNA production
PATENT ASSIGNEE: Boehr.Ingelheim; Genentech; Univ.N.Carolina 1993
PATENT NUMBER: EP 535576 PATENT DATE: 930407 WPI ACCESSION NO.: 93-110900 (9314)
PRIORITY APPLIC. NO.: US 864758 APPLIC. DATE: 920407
NATIONAL APPLIC. NO.: EP 92116577 APPLIC. DATE: 920928
LANGUAGE: German
ABSTRACT: A new conjugate for nucleic acid transport into a higher eukaryote cell comprises a virus vector as an internalizing factor bound to a substance with nucleic acid affinity substance by an antibody, so that it enters the endosome of the cells as part of a nucleic acid-conjugate complex, which empties the endosome content into the cytoplasm. The following are also new: a complex of nucleic acid and the conjugate; a method for transformation of eukaryotic cells using the conjugate; a pharmaceutical composition containing the conjugate; and a transfection kit containing the conjugate. The antibody is preferably a monoclonal antibody which binds to an adeno virus hexon region. The substance with nucleic acid affinity is a polycation, preferably polylysine. The method is useful in *gene* *therapy* of e.g. cystic fibrosis, low density lipoprotein receptor deficiency or cancer, or for introduction of sequences encoding antisense RNA. The use of viruses which target the endosome means that the target genes do not reach lysosomes (where they are degraded). (38pp)
DESCRIPTORS: new higher eukaryote transfection method, *DNA*, polycation, *antibody* conjugate complex, adeno virus vector, endosome localization, appl. *gene* *therapy*, antisense RNA delivery gene transmission cloning
SECTION: PHARMACEUTICALS-Clinical Genetic Techniques; GENETIC ENGINEERING AND FERMENTATION-Nucleic Acid Technology (D7,A1)

4/9/50 (Item 42 from file: 357)
DIALOG(R)File 357:Derwent Biotechnology Abs

121020 DBA Accession No.: 91-08662 PATENT
Production of chimeric antibodies - chimeric antibody construction by trans-splicing DNA encoding a first portion of the *antibody* with *DNA* encoding a second portion
PATENT ASSIGNEE: Loyola-Univ.Chicago 1991
PATENT NUMBER: WO 9105856 PATENT DATE: 910502 WPI ACCESSION NO.: 91-148734 (9120)
PRIORITY APPLIC. NO.: US 421550 APPLIC. DATE: 891013
NATIONAL APPLIC. NO.: WO 90US5797 APPLIC. DATE: 901010
LANGUAGE: English
ABSTRACT: A process for producing a chimeric antibody (CAb) or CAb-encoding nucleic acid is claimed comprising: i. introducing DNA encoding a 2nd portion of a CAb into a cell expressing DNA encoding a 1st portion of a CAb; iii. combining the 2 portions within the cell by trans-splicing; iv. culturing the cell; and v. selecting a CAb comprising the 1st and 2nd portion from the medium or isolating a CAb-encoding nucleic acid from the cells. Also claimed are purified products from the process. The 2nd portion may be introduced by B-lymphocyte fusion. The trans-splicing of immunoglobulin (Ig) heavy chains requires that a

B-cell simultaneously expresses 2 Ig heavy chains. By utilizing trans-splicing, a single DNA construct containing the desired Ig constant region can be used to produce chimeric Igs with different specificities. Trans-splicing eliminates the need to isolate and clone the variable region genes to be expressed in association with a desired constant region gene. CAbs may be obtained which have the antigen binding specificity of an antibody and the biological activity of e.g. an enzyme, toxin, lymphokine or cellular receptor. (41pp)

DESCRIPTORS: chimeric antibody prep., in vitro trans-splicing of *antibody* *DNA* e.g. immunoglobulin heavy chain with e.g. enzyme, toxin, lymphokine, cell receptor, B-lymphocyte fusion, antibody engineering, pot. appl. in disease diagnosis, clinical medicine, *gene* *therapy*, etc. immunotoxin gene transmission bispecific antibody

SECTION: Pharmaceuticals-Other; Cell Culture-Animal Cell Cul

8/9/3 (Item 3 from file: 5)
DIALOG(R)File 5:BIOSIS PREVIEWS(R)

10099321 BIOSIS Number: 95099321

SPECIFIC RECOGNITION OF ANTIBODY-OLIGONUCLEOTIDE CONJUGATES BY RADIOLABELED ANTISENSE NUCLEOTIDES A NOVEL APPROACH FOR TWO-STEP RADIOIMMUNOTHERAPY OF CANCER

KUIJPERS W H A; BOS E S; KASPERSEN F M; VEENEMAN G H; VAN BOECKEL C A A
AKZO PHARMA DIV., ORGANON INTERNATIONAL BV, P.O. BOX 20, 5340 BH OSS, NETH.

BIOCONJUGATE CHEM 4 (1). 1993. 94-102. CODEN: BCCHE
Language: ENGLISH

MF

One of the major challenges in radioimmunotherapy is the specific delivery of radioisotopes to tumor cells while minimizing normal tissue radiation. In this respect, the application of two-step pretargeting schemes generally leads to more favorable tumor to normal tissue uptake ratios than direct administration of radioimmunoconjugates. In this study, we present the specific hybridization of complementary DNA fragments as a novel recognition mechanism in pretargeting. Briefly, our stratgegy involves first administration of *antibody*-*DNA* *conjugate*, followed by *targeting* with radiolabeled complementary DNA (antisense DNA). Complementary oligodeoxynucleotides (14-mers, Tm = 57.degree. C), in which part of the phosphodiesters has been replaced by methylphosphonates (to ensure stability against nucleases), were prepared on a DNA synthesizer. The oligonucleotides were further derivatized via a uridine moiety at their 5'-end in such a way that radiolabeling or conjugation with antibodies could be accomplished. Both a murine IgG (anti-hCG) and the human anti-tumor IgM 16.88 were conjugted with one to three oligonucleotides via the heterobifunctional cross-linker SMCC. Incubation of these immunoconjugates with the radiolabeled antisense DNA revealed specific hybridization with the antibody-linked oligonucleotides. Antigen binding studies performed with antigen-coated matrices showed that the immunoreactivity of the *antibody*-*DNA* *conjugate* is preserved. Moreover, it is demonstrated that the radiolabeled DNA is still capable of hybridizing selectively with the oligonucleotides of the immunoconjugate, when the latter is bound to its antigen.

Descriptors/Keywords: MURINE IMMUNOGLOBULIN G *CONJUGATE* HUMAN ANTITUMOR IMMUNOGLOBULIN M *ANTIBODY*-*DNA* *CONJUGATE* SYNTHETIC METHOD POTENTIAL THERAPEUTIC METHOD IMMUNOLOGIC METHOD

Concept Codes:
*03506 Genetics and Cytogenetics-Animal
*03508 Genetics and Cytogenetics-Human
*06504 Radiation-Radiation and Isotope Techniques
*10062 Biochemical Studies-Nucleic Acids, Purines and Pyrimidines
*10506 Biophysics-Molecular Properties and Macromolecules
*12512 Pathology, General and Miscellaneous-Therapy (1971-)
*22018 Pharmacology-Immunological Processes and Allergy
*24003 Neoplasms and Neoplastic Agents-Immunology
*24008 Neoplasms and Neoplastic Agents-Therapeutic Agents; Therapy
10064 Biochemical Studies-Proteins, Peptides and Amino Acids
10068 Biochemical Studies-Carbohydrates

Biosystematic Codes:
86215 Hominidae
86375 Muridae

Super Taxa:
Animals; Chordates; Vertebrates; Mammals; Primates; Humans; Nonhuman

Vertebrates; Nonhuman Mammals; Rodents

8/9/4 (Item 4 from file: 5)
DIALOG(R)File 5:BIOSIS PREVIEWS(R)

9590741 BIOSIS Number: 94095741
CATIONIC LIPOSOMES ENHANCE *TARGETED* DELIVERY AND EXPRESSION OF EXOGENOUS DNA MEDIATED BY N-TERMINAL MODIFIED POLY-L-LYSINE-ANTIBODY *CONJUGATE* IN MOUSE LUNG ENDOTHELIAL CELLS
TRUBETSKOY V S; TORCHILIN V P; KENNEL S; HUANG L
CENTER IMAGING PHARMACEUTICAL RES., MASSACHUSETTS GENERAL HOSPITAL, BUILDING 149, 13TH ST., CHARLESTOWN, MASS. 02129.
BIOCHIM BIOPHYS ACTA 1131 (3). 1992. 311-313. CODEN: BBACA
Full Journal Title: Biochimica et Biophysica Acta
Language: ENGLISH
A new and improved system for *targeted* gene delivery and expression is described. Transfection efficiency of N-terminal modified poly(L-lysine) (NPLL) conjugated with anti-thrombomodulin antibody 34A can be improved by adding to the system a lipophilic component, cationic liposomes. *DNA*, *antibody* *conjugate* and cationic liposomes form a ternary electrostatic *complex* which preserves the ability to bind specifically to the *target* cells. At the same time the addition of liposomes enhance the specific transfection efficiency of *antibody*-polylysine/*DNA* binary *complex* by 10 to 20-fold in mouse lung endothelial cells in culture.
Descriptors/Keywords: *TARGETED* GENE DELIVERY NEW METHOD IMMUNOLOGICAL METHOD TRANSFECTION EFFICIENCY
Concept Codes:
*03506 Genetics and Cytogenetics-Animal
*10052 Biochemical Methods-Nucleic Acids, Purines and Pyrimidines
*10508 Biophysics-Membrane Phenomena
*34502 Immunology and Immunochemistry-General; Methods
10062 Biochemical Studies-Nucleic Acids, Purines and Pyrimidines
10064 Biochemical Studies-Proteins, Peptides and Amino Acids
16001 Respiratory System-General; Methods
Biosystematic Codes:
86375 Muridae
Super Taxa:
Animals; Chordates; Vertebrates; Nonhuman Vertebrates; Mammals; Nonhuman Mammals; Rodents

8/9/8 (Item 1 from file: 73)
DIALOG(R)File 73:EMBASE

9496759 EMBASE No: 95058278
Application of chimeric antibody for cancer immunotherapy
Yamaguchi T.; Takahashi T.; Kitamura K.; Otsuji E.
Department of Surgery, Kyoto Prefectural University of Med., 465 Kajii-cho, Hirokoji-Agaru, Kamigyo-ku, Kyoto 602 Japan
Biotherapy (Japan) , 1995, 9/1 (47-50) CODEN: BITPE ISSN: 0914-2223
LANGUAGES: Japanese SUMMARY LANGUAGES: Japanese; English
SUBFILES: 016; 026; 048
Immunotargeting chemotherapy using immunoconjugate of mouse monoclonal antibody and anti-cancer drugs has many problems awaiting solution. Especially production of human antibody against mouse monoclonal antibody

inhibits the specific accumulation of immunoconjugate in cancer tissues. To overcome this unfavorable immunological reaction, humanized antibody was developed using recombinant *DNA* technology. Chimeric *antibody* composed of variable regions of mouse specific monoclonal antibody A7 and constant region of human IgG was successfully produced by yeast. The anti-cancer drug neocarzinostatin was bound to Fab fragment of chimeric antibody without losing either antibody activity or anticancer activity. This *conjugate* (Ch-A7-NCS) showed a specific accumulation in cancer tissues and a superior anticancer effect on antigen-positive colon cancer cells. The acute toxicity of Ch-A7-NCS was less than that of aqueous solution of neocarzinostatin. Phase 1 study of Ch-A7-NCS suggested that the maximum tolerable dose of Ch-A7-NCS is around 40,000 units/body, and no serious side effects were found. The phase 2 clinical trial will start in the near future.

EMTAGS:
Therapy 0160; Chemical procedures 0107; Pharmacokinetics 0194; Mammal 0738; Human 0888; Clinical article 0152; Article 0060
DRUG DESCRIPTORS:
*chimeric antibody; *zinostatin
monoclonal antibody
MEDICAL DESCRIPTORS:
*colon cancer--drug therapy--dt; *cancer immunotherapy
drug conjugation; drug *targeting*; human; clinical article; phase 1 clinical trial; article
EMCLAS DRUG CODES:
03700000000

CAS REGISTRY NO.: 9014-02-2

8/9/46 (Item 3 from file: 357)
DIALOG(R)File 357:Derwent Biotechnology Abs

151782 DBA Accession No.: 93-09834 PATENT
Virus inactivated cell-binding receptor and monoclonal antibody *complex* - recombinant bispecific antibody application in virus vector *targeting* into mammal cell
PATENT ASSIGNEE: Thera-Gene 1993
PATENT NUMBER: WO 9309221 PATENT DATE: 930513 WPI ACCESSION NO.: 93-167689 (9320)
PRIORITY APPLIC. NO.: SE 913183 APPLIC. DATE: 911030
NATIONAL APPLIC. NO.: WO 92SE745 APPLIC. DATE: 921028
LANGUAGE: English
ABSTRACT: A *complex* between a virus with an inactivated cell-binding receptor and an antigen (Ag)-binding substance is new. The Ag-binding substance can interact with a specific Ag on a mammalian cell surface, different from the cellular structure which other wise mediates binding of the virus to the cell surface. The Ag-binding substance is preferably a monoclonal antibody or a fragment prepared by chemical synthesis or expression of *antibody* genes or *DNA* sequences containing information derived from the genes. The Ag-binding substance may be a bispecific antibody, binding to a virus and cellular Ag. The antibody binding sites are expressed on the viral surface of the *complex* following cloning of *antibody* genes or *DNA* sequences, encoding *antibody* -binding structures, into the viral genome. The viral cell receptor is inactivated by chemical means, a specific

antibody or gene technology. Genes for the viral cell receptor may be replaced by antibody genes. The *complex* may be used for *targeted* delivery of viral vectors to mammal cells and it allows specific cell *targeting* by viral vectors or infectious viruses. (16pp)
DESCRIPTORS: virus inactivated cell-binding receptor, monoclonal antibody *complex*, recombinant bispecific antibody, appl. virus vector *targeting* into mammal cell
SECTION: PHARMACEUTICALS-Antibodies; GENETIC ENGINEERING AND FERMENTATION-Nucleic Acid Technology (D6,A1)

8/9/51 (Item 8 from file: 357)
DIALOG(R)File 357:Derwent Biotechnology Abs

096842 DBA Accession No.: 89-14833 PATENT
Integration of foreign DNA into cell culture - by conjugating the foreign DNA with a *target* specific antibody and binding to the cell
PATENT ASSIGNEE: U.S.Dept.Health-Human-Serv. 1989
PATENT NUMBER: US 7255837 PATENT DATE: 890725 WPI ACCESSION NO.: 89-285626 (8939)
PRIORITY APPLIC. NO.: US 255837 APPLIC. DATE: 881011
NATIONAL APPLIC. NO.: US 255837 APPLIC. DATE: 881011
No pat issued
LANGUAGE: English
ABSTRACT: A method for integrating foreign DNA into cells in a tissue-specific manner comprises: (1) preparing a *conjugate* of foreign *DNA* with an *antibody*, which binds to a surface antigen of the cell into which the foreign DNA is introduced; and (2) binding the *conjugate* and the cell into which the DNA is to be integrated. The transformed cells produce recombinant protein. The new method allows *target* -specific DNA delivery and is applicable to in vivo transformation and gene therapy. The method can also be used for stable in vitro integration of DNA into cells. In an example, a plasmid encoding kanamycin-kinase (EC-2.7.1.95) was dissolved in buffer containing 50 mM benzoquinone in ethanol in the dark for 1 hr and then passed through a G25 column and prewashed in Saccharomyces cerevisiae RNA. The activated DNA was incubated with hamster monoclonal antibody 145-2C11 (specific for mouse CD3 antigen) and then with the 2B4 cell line (a CD3- mouse T-lymphocyte hybridoma). G418-resistant cells were grown for 4 wk. Southern blotting revealed that the kanamycin-kinase gene had stably integrated into the host cell's DNA. (16pp)
E.C. NUMBERS: 2.7.1.95
DESCRIPTORS: cell culture e.g. CD3-specific hamster hybridoma transformation, gene transmission using antibody *conjugate*, appl. in gene therapy mammal cell culture
SECTION: Microbiology-Genetics; Pharmaceuticals-Other (A1,D5)

8/9/53 (Item 2 from file: 399)
DIALOG(R)File 399:CA SEARCH(R)

116091374 CA: 116(10)91374c PATENT
Nucleic acid complexes of antibody-polycation conjugates
INVENTOR(AUTHOR): Birnstiel, Max L.; Cotten, Matthew; Wagner, Ernst
LOCATION: Germany,
ASSIGNEE: Boehringer Ingelheim International G.m.b.H.; Genentech, Inc.
PATENT: PCT International ; WO 9117773 A1 DATE: 911128
order

APPLICATION: WO 91EP875 (910510) *AT 901110 (900518) *DE 4110410 (910329)
PAGES: 64 pp. CODEN: PIXXD2 LANGUAGE: German CLASS: A61K-047/48A; C12N-015/87B DESIGNATED COUNTRIES: JP; US DESIGNATED REGIONAL: AT; BE; CH ; DE; DK; ES; FR; GB; GR; IT; LU; NL; SE
SECTION:
CA263005 Pharmaceuticals
IDENTIFIERS: DNA complex antibody polycation conjugate, T cell surface protein targeting
DESCRIPTORS:
Antibodies...
antiCD4, conjugates with polylysine90, complexes with DNA, for DNA import and expression, in T-cell lineage cells
Nucleic acids,conjugates...
complexes with protein-polycation, targeted to cellular surface proteins of T-cell lineage cells
Protamines...
conjugates with polycations, complexes with nucleic acids, for targeting to surface protein of T-cell lineage cells
Deoxyribonucleic acids,complexes...
with antiCD4 antibody-polylysine90 conjugates, for DNA import and expression, in T-cell lineage cells
Histones,conjugates...
with polycations, complexes with nucleic acids, for targeting to surface protein of T-cell lineage cells
CAS REGISTRY NUMBERS:
25104-18-1D conjugate with antiCD4 antibodies, complexes with DNA, for DNA import and expression, in T-cell lineage
38000-06-5 for DNA import and expression, in T-cell lineage

15/9/10 (Item 10 from file: 5)
DIALOG(R)File 5:BIOSIS PREVIEWS(R)

7103291 BIOSIS Number: 88026036
NUCLEOTIDE *SEQUENCE* OF A COMPLEMENTARY DNA ENCODING RAT PROTAMINE AND THE HAPLOID EXPRESSION OF THE GENE DURING RAT SPERMATOGENESIS
KLEMM U; LEE C-H; BURFEIND P; HAKE S; ENGEL W
INSTITUT FUER HUMANGENETIK DER UNIVERSITAET GOETTINGEN.
BIOL CHEM HOPPE-SEYLER 370 (4). 1989. 293-302. CODEN: BCHSE
Full Journal Title: Biological Chemistry Hoppe-Seyler
Language: ENGLISH
The nucleotide *sequence* of a 342-base cDNA encoding the rat protamine had been determined. This insert, isolated from a rat testis cDNA library, encodes a polypeptide of 50 amino acids of which 29 are arginine, 9 are cysteine and 2 are tyrosine. The insert contains the complete 3'-noncoding region of 170 bases and 18 bases of the 5'-noncoding region. Hybridization of the protamin cDNA with the RNA prepared from testes of prepubertal and sexually mature rats revealed that protamine mRNA is first detectable as a 600 nucleotide long molecule in the 35-day old testis containing around 15% of round spermatids but not in testis of younger animals. The RNA of 50-day old and sexually mature rats was found to contain a second protamine mRNA which is around 500 nucleotides in length. Hybridization of the protamine cDNA with the RNA of isolated spermatids of the mature testis resulted in 2 prominent hybridization signals (600 and 500 bp) while the faint signal obtained with the RNA of pachytene spermatocytes (600 bp) was found to be due to contamination of the cell preparation by spermatids. After digestion of the mRNA with ribonuclease H a single hybridization band even smaller than 500 nucleotides was obtained. As demonstrated on testis sections the transcripts are confined to the central layers of the tubuli seminiferi corresponding to the spatial arrangement of postmeiotic cells. The results indicate that the *protamine* *gene* in the rat is postmeiotically expressed and that the mRNA undergoes posttranscriptional processing that includes a reduction in molecular size with respect to the poly-(A)+ tail.
Descriptors/Keywords: MESSENGER RNA NUCLEOTIDE *SEQUENCE* AMINO ACID *SEQUENCE* MOLECULAR *SEQUENCE* DATA
Concept Codes:
*02506 Cytology and Cytochemistry-Animal
*03506 Genetics and Cytogenetics-Animal
*10062 Biochemical Studies-Nucleic Acids, Purines and Pyrimidines
*10064 Biochemical Studies-Proteins, Peptides and Amino Acids
*10506 Biophysics-Molecular Properties and Macromolecules
*16504 Reproductive System-Physiology and Biochemistry
10052 Biochemical Methods-Nucleic Acids, Purines and Pyrimidines
10054 Biochemical Methods-Proteins, Peptides and Amino Acids
Biosystematic Codes:
86375 Muridae
Super Taxa:
Animals; Chordates; Vertebrates; Nonhuman Vertebrates; Mammals; Nonhuman Mammals; Rodents

15/9/15 (Item 15 from file: 5)
DIALOG(R)File 5:BIOSIS PREVIEWS(R)

6581652 BIOSIS Number: 86048203
SEQUENCE HOMOLOGIES IN THE MOUSE PROTAMINE 1 AND 2 GENES

JOHNSON P A; PESCHON J J; YELICK P C; PALMITER R D; HECHT N B
DEP. BIOL., TUFTS UNIV., MEDFORD, MASS. 02155.
BIOCHIM BIOPHYS ACTA 950 (1). 1988. 45-53. CODEN: BBACA
Full Journal Title: Biochimica et Biophysica Acta
Language: ENGLISH

QD1

To identify candidates for cis-acting sequences that regulate the stage and cell-specific expression of the two coordinately regulated protamine genes in the mouse, genomic clones were isolated and the nucleotide sequences of the 5' flanking regions and coding regions were compared. Unlike most histone genes and the multigene family of trout protamine genes which are intronless, each mouse *protamine* *gene* has a single short intervening *sequence* . Although the coding regions do not share significant nucleotide homology, the 5' flanking regions contain several short homologous sequences that may be involved in gene regulation. An additional shared *sequence* is present in the 3' untranslated region surrounding the poly(A) addition signal in both genes.

19/9/2 (Item 2 from file: 5)
DIALOG(R)File 5:BIOSIS PREVIEWS(R)

11454934 BIOSIS Number: 98054934

Analysis of Sequences Required for the Cytotoxic Action of a Chimeric Toxin Composed of *Pseudomonas* *Exotoxin* and Transforming Growth Factor alpha

Kihara A; Pastan I
Lab. Mol. Biol., Div. Cancer Biol., Diagnosis Cent., Natl. Cancer Inst., Natl. Inst. Health, 9000 Rockville Pike, Build. 37, Room 4E16, Bethesda, MD 20892, USA

Bioconjugate Chemistry 5 (6). 1994. 532-538.
Full Journal Title: Bioconjugate Chemistry
ISSN: 1043-1802
Language: ENGLISH
Print Number: Biological Abstracts Vol. 099 Iss. 003 Ref. 039478

Chimeric toxins composed of transforming growth factor alpha fused to mutant forms of *Pseudomonas* *exotoxin* bind to the EGF receptor and kill cells bearing these receptors. In early experiments, the binding domain of *Pseudomonas* *exotoxin* was deleted and replaced with TGF-alpha to make TGF-alpha-PE40. This chimeric toxin required proteolytic processing within the target cell to be converted to its active form (Siegall et al. (1989) FASEB J. 3, 2647-2652). Subsequently, recombinant toxins that do not require proteolytic processing were constructed by inserting TGF-alpha near the carboxyl terminus of *domain* *III* and deleting toxin residues up to the processing site at position 280. In addition, the carboxyl terminus of this toxin was converted from REDLK to KDEL to increase its activity. Recombinant toxins of this type, termed PE37/TGF-alpha/KDEL, are about 100-fold more potent than TGF-alpha-PE40. To determine if other sequences can be removed from such chimeric toxins to make a smaller molecule that can penetrate tissues better, we have carried out a deletion analysis of sequences present within domains II and Ib. We find that all of domain Ib and a portion of domain II can be deleted without significant loss of cytotoxic activity, but larger deletions extending further into domain II lose cytotoxic activity. We also find that inserting a small linking peptide (Gly)-4Ser between residual sequences in domain II and *domain* *III* , in molecules with diminished cytotoxic activity, enhances cytotoxicity suggesting that one role of domain Ib is to prevent undesirable interactions between domains II and III. These new chimeric toxins are very active on A431 epidermoid carcinoma cells which contain many EGF receptors. One of these was also tested in animals and showed strong antitumor activity against A431 tumors growing in nude mice.

Descriptors/Keywords: RESEARCH ARTICLE; PSEUDOMONAS; A431 EPIDERMOID CARCINOMA CELL; EPIDERMAL GROWTH FACTOR RECEPTOR; POTENTIAL ANTINEOPLASTIC THERAPY

Concept Codes:
*10062 Biochemical Studies-Nucleic Acids, Purines and Pyrimidines
*10064 Biochemical Studies-Proteins, Peptides and Amino Acids
*10506 Biophysics-Molecular Properties and Macromolecules
*10508 Biophysics-Membrane Phenomena
*12512 Pathology, General and Miscellaneous-Therapy (1971-)
*17002 Endocrine System-General
*22501 Toxicology-General; Methods and Experimental
*24004 Neoplasms and Neoplastic Agents-Pathology; Clinical Aspects; Systemic Effects
*24008 Neoplasms and Neoplastic Agents-Therapeutic Agents; Therapy
*31000 Physiology and Biochemistry of Bacteria

Biosystematic Codes:
06508 Pseudomonadaceae (1992-)
Super Taxa:
Microorganisms; Bacteria; Eubacteria

19/9/3 (Item 3 from file: 5)
DIALOG(R)File 5:BIOSIS PREVIEWS(R)

11406912 BIOSIS Number: 98006912
Primate Antibody Response to Immunotoxin: Serological and Computer-Aided Analysis of Epitopes on a Truncated Form of *Pseudomonas* *Exotoxin*
Roscoe D M; Jung S-H; Benhar I; Pai L; Lee B K; Pastan I
Lab. Mol. Biol., DCBDC, NCI, Natl. Inst. Health, Build. 37, Room 4E16, 9000 Rockville Pike, Bethesda, MD 20892, USA
Infection and Immunity 62 (11). 1994. 5055-5065.
Full Journal Title: Infection and Immunity
ISSN: 0019-9567
Language: ENGLISH
Print Number: Biological Abstracts Vol. 099 Iss. 001 Ref. 006912
NLysPE38 is a 38-kDa derivative of *Pseudomonas* *exotoxin* (PE) in which domain Ia (amino acids 1 to 252) and part of domain Ib (365 to 380) are deleted and an 11-amino-acid N-terminal peptide is added. LMB-1 is an immunotoxin in which the monoclonal antibody B3 is coupled to NLysPE38 near its N terminus. LMB-7 is a single-chain immunotoxin in which the Fv fragment of B3 is fused to PE38. To identify the antigenic regions of PE38,12 polyclonal serum samples from monkeys immunized with the immunotoxins LMB-1 (six monkeys) and LMB-7 (six monkeys) were tested for their reactivity to a panel of 120 synthetic, overlapping peptides representing the amino acid sequence of NLysPE38. The antibody responses to peptides were similar among the 12 serum specimens, identifying several major immunodominant B-cell epitopes. Predominant reactivity was seen in six locations: amino acids 272 to 287, 341 to 359, 504 to 516, 540 to 564, and 573 to 591 and the C-terminal amino acids 591 to 613. The sera did not react with approximately 75% of the peptides. Furthermore, a computer-aided analysis was done to predict the immunologically relevant areas and revealed the same antigenic regions defined by serum reactivity to peptides. Competition enzyme-linked immunosorbent assays and neutralization assays were performed with domain II, III or III plus Ib of PE38 and confirmed the immunodominance of *domain* *III*. To analyze the role of specific amino acids in antibody binding, individual amino acids of PE38 with large accessible surface areas were altered by site-directed mutagenesis. These results also show that the predicted areas of immunogenicity agree with the reactivity of the anti-PE38 antibodies to peptides and to the mutants of PE.
Descriptors/Keywords: RESEARCH ARTICLE; PSEUDOMONAS; MONKEY; LMB-1; LMB-7; ANTIBODY BINDING; B-CELL EPITOPES; IMMUNOGENICITY; MOLECULAR SEQUENCE DATA; AMINO ACID SEQUENCE
Concept Codes:
*10506 Biophysics-Molecular Properties and Macromolecules
*15002 Blood, Blood-Forming Organs and Body Fluids-Blood and Lymph Studies
*15004 Blood, Blood-Forming Organs and Body Fluids-Blood Cell Studies
*15008 Blood, Blood-Forming Organs and Body Fluids-Lymphatic Tissue and Reticuloendothelial System
*22501 Toxicology-General; Methods and Experimental
*34504 Immunology and Immunochemistry-Bacterial, Viral and Fungal

*34508 Immunology and Immunochemistry-Immunopathology, Tissue Immunology
*36002 Medical and Clinical Microbiology-Bacteriology
00530 General Biology-Information, Documentation, Retrieval and Computer Applications
02506 Cytology and Cytochemistry-Animal
04500 Mathematical Biology and Statistical Methods
10064 Biochemical Studies-Proteins, Peptides and Amino Acids
10066 Biochemical Studies-Lipids
10068 Biochemical Studies-Carbohydrates
Biosystematic Codes:
06508 Pseudomonadaceae (1992-)
86190 Primates-Unspecified
Super Taxa:
Microorganisms; Bacteria; Eubacteria; Animals; Chordates; Vertebrates; Nonhuman Vertebrates; Mammals; Nonhuman Mammals; Primates; Nonhuman Primates

19/9/4 (Item 4 from file: 5)
DIALOG(R)File 5:BIOSIS PREVIEWS(R)

11315473 BIOSIS Number: 97515473
Correction of PREVIEWS 97374704. B3 (Fab)-PE38-M: A recombinant immunotoxin in which a mutant form of *Pseudomonas* *exotoxin* is fused to the fab fragment of monoclonal antibody B3. Addition of author name. Erratum published in CANCER RESEARCH Vol. 54. Iss. 16. 1994. p. 4555
Choe M; Pai L H; Webber K O; Pastan I
Lab. Mol. Biol., Natl. Cancer Inst., NIH, 9000 Rockville Pike, Build. 37, Room 4E16, Bethesda, MD 20892, USA
Cancer Research 54 (13). 1994. 3460-3467.
Full Journal Title: Cancer Research
ISSN: 0008-5472
Language: ENGLISH
Print Number: Biological Abstracts Vol. 098 Iss. 011 Ref. 151212

Recombinant immunotoxins were made by fusing the Fab domain of monoclonal antibody (MAb) B3 to PE38-M, a truncated mutant form of *Pseudomonas* *exotoxin* (PE). The recombinant toxins were made in Escherichia coli by fusing genes encoding the antibody domains to a gene encoding the mutant form of PE. MAb B3 binds to a carbohydrate antigen found on many kinds of carcinomas. Immunotoxins in which MAb B3 has been chemically coupled to recombinant forms of PE have been shown to be very active cytotoxic agents. PE has also been targeted to tumor cells by replacing the cell-binding domain of PE (domain I) with a single-chain antibody to make a single-chain immunotoxin. In the current study, PE38-M, a mutant form of PE, with a deletion of the cell-binding domain (amino acids 1-252) as well as mutations in *domain* *III* and some nonessential sequences in domain 1b (amino acids 365-380), was fused to the light chain of MAb B3. This protein was renatured in the presence of the Fd fragment of MAb B3 to produce a Fab-toxin fusion protein. Alternatively, the Fd fragment of MAb B3 was fused to PE38-M and combined with the light chain. Both types of B3(Fab)-PE38-M were just as active on target cells as previously described single-chain immunotoxins. Furthermore, the B3(Fab)-PE38-M has two advantages over single-chain immunotoxins. One is that the yield of recombinant Fab-toxin is very high, with 10-22% of the starting protein recovered as cytotoxically active immunotoxin after chromatographic purification. The second is that the B3(Fab)-PE38-M has a much longer

survival in the circulation of mice with a t-1/2beta of apprx 5 h.
Descriptors/Keywords: CORRECTED ARTICLE; RESEARCH ARTICLE; PSEUDOMONAS; ESCHERICHIA COLI; HUMAN; MOUSE; EPIDERMOID CARCINOMA; IMMUNOTHERAPY
Concept Codes:
*18506 Integumentary System-Pathology
*22018 Pharmacology-Immunological Processes and Allergy
*22020 Pharmacology-Integumentary System, Dental and Oral Biology
*24003 Neoplasms and Neoplastic Agents-Immunology
*24008 Neoplasms and Neoplastic Agents-Therapeutic Agents; Therapy
*34508 Immunology and Immunochemistry-Immunopathology, Tissue Immunology
10054 Biochemical Methods-Proteins, Peptides and Amino Acids
10056 Biochemical Methods-Lipids
10058 Biochemical Methods-Carbohydrates
10064 Biochemical Studies-Proteins, Peptides and Amino Acids
10066 Biochemical Studies-Lipids
10068 Biochemical Studies-Carbohydrates
10506 Biophysics-Molecular Properties and Macromolecules
11107 Anatomy and Histology, General and Comparative-Regeneration and Transplantation (1971-)
12100 Movement (1971-)
12512 Pathology, General and Miscellaneous-Therapy (1971-)
13004 Metabolism-Carbohydrates
13006 Metabolism-Lipids
13012 Metabolism-Proteins, Peptides and Amino Acids
15002 Blood, Blood-Forming Organs and Body Fluids-Blood and Lymph Studies
22003 Pharmacology-Drug Metabolism; Metabolic Stimulators
22005 Pharmacology-Clinical Pharmacology (1972-)
22501 Toxicology-General; Methods and Experimental
31000 Physiology and Biochemistry of Bacteria
31500 Genetics of Bacteria and Viruses
Biosystematic Codes:
06508 Pseudomonadaceae (1992-)
06702 Enterobacteriaceae (1992-)
86215 Hominidae
86375 Muridae
Super Taxa:
Microorganisms; Bacteria; Eubacteria; Animals; Chordates; Vertebrates; Mammals; Primates; Humans; Nonhuman Vertebrates; Nonhuman Mammals; Rodents

19/9/5 (Item 5 from file: 5)
DIALOG(R)File 5:BIOSIS PREVIEWS(R)

11315339 BIOSIS Number: 97515339
Small chimeric toxins containing only transforming growth factor alpha and *domain* *III* of *Pseudomonas* *exotoxin* with good antitumor activity in mice
Kihara A; Pastan I
Lab. Mol. Biol., Natl. Cancer Inst., NIH, 9000 Rockville Pike, Bldg. 37, Room 4E16, Bethesda, MD 20892, USA
Cancer Research 54 (19). 1994. 5154-5159.
Full Journal Title: Cancer Research
ISSN: 0008-5472
Language: ENGLISH

Print Number: Biological Abstracts Vol. 098 Iss. 011 Ref. 151078
Chimeric toxins composed of transforming growth factor a (TGF-alpha) fused to mutant forms of *Pseudomonas* *exotoxin* (PE) bind to the epidermal growth factor receptor and kill cells bearing epidermal growth factor receptors. Initially, the binding domain (Ia; amino acids 1-252) of PE was deleted and replaced with TGF-alpha to make TGF-alpha-PE40 in which TGF-alpha is fused to domains II, Ib, and III of PE (amino acids 253-613). That drug is currently undergoing clinical study for the intravesical therapy of bladder cancer. To generate smaller molecules that would have increased tumor penetration, several deletion mutants were constructed. In one of these, TGF-alpha was inserted near the carboxyl terminus of PE, and residues in domains II and Ib of PE (amino acids 253-279 and 365-380) were deleted so that the chimeric toxin did not need to be cleaved by an intracellular protease to be activated (Theuer el al., J. Biol. Chem., 267: 16872-16877, 1992). We have now constructed chimeric toxins which contain only *domain* *III*, yet still exhibit high cytotoxic activity on epidermal growth factor receptor-containing cells and produce substantial tumor regressions in mice bearing a human xenograft. The high cytotoxic activity of these severely truncated toxins provides new insights on the proposed functions of domains II and III of PE.
Descriptors/Keywords: RESEARCH ARTICLE; PSEUDOMONAS; POTENTIAL ANTINEOPLASTIC APPLICATION
Concept Codes:
*12512 Pathology, General and Miscellaneous-Therapy (1971-)
*17002 Endocrine System-General
*22501 Toxicology-General; Methods and Experimental
*24008 Neoplasms and Neoplastic Agents-Therapeutic Agents; Therapy
*31000 Physiology and Biochemistry of Bacteria
10060 Biochemical Studies-General
10064 Biochemical Studies-Proteins, Peptides and Amino Acids
Biosystematic Codes:
06702 Enterobacteriaceae (1992-)
86375 Muridae
Super Taxa:
Microorganisms; Bacteria; Eubacteria; Animals; Chordates; Vertebrates; Nonhuman Vertebrates; Mammals; Nonhuman Mammals; Rodents

19/9/6 (Item 6 from file: 5)
DIALOG(R)File 5:BIOSIS PREVIEWS(R)

11174704 BIOSIS Number: 97374704
B3 (Fab)-PE38-M: A recombinant immunotoxin in which a mutant form of *Pseudomonas* *exotoxin* is fused to the fab fragment of monoclonal antibody B3
Choe M; Webber K O; Pastan I
Lab. Molecular Biol., National Cancer Inst., NIH, 9000 Rockville Pike, Building 37, Room 4E16, Bethesda, MD 20892, USA
Cancer Research 54 (13). 1994. 3460-3467.
Full Journal Title: Cancer Research
ISSN: 0008-5472
Language: ENGLISH
Print Number: Biological Abstracts Vol. 098 Iss. 005 Ref. 063193
Recombinant immunotoxins were made by fusing the Fab domain of monoclonal antibody (MAb) B3 to PE38-M, a truncated mutant form of *Pseudomonas* *exotoxin* (PE). The recombinant toxins were made in Escherichia coli by fusing genes encoding the antibody domains to a gene encoding the mutant

form of PE. MAb B3 binds to a carbohydrate antigen found on many kinds of carcinomas. Immunotoxins in which MAb B3 has been chemically coupled to recombinant forms of PE have been shown to be very active cytotoxic agents. PE has also been targeted to tumor cells by replacing the cell-binding domain of PE (domain I) with a single-chain antibody to make a single-chain immunotoxin. In the current study, PE38-M, a mutant form of PE, with a deletion of the cell-binding domain (amino acids 1-252) as well as mutations in *domain* *III* and some nonessential sequences in domain 1b (amino acids 365-380), was fused to the light chain of MAb B3. This protein was renatured in the presence of the Fd fragment of MAb B3 to produce a Fab-toxin fusion protein. Alternatively, the Fd fragment of MAb B3 was fused to PE38-M and combined with the light chain. Both types of B3(Fab)-PE38-M were just as active on target cells as previously described single-chain immunotoxins. Furthermore, the B3(Fab)-PE38-M produced complete remissions of human tumor xenografts growing in nude mice. B3(Fab)-PE38-M has two advantages over single-chain immunotoxins. One is that the yield of recombinant Fab-toxin is very high, with 10-22% of the starting protein recovered as cytotoxically active immunotoxin after chromatographic purification. The second is that the B3(Fab)-PE38-M has a much longer survival in the circulation of mice with a t-1/2beta of apprx 5 h.

Descriptors/Keywords: RESEARCH ARTICLE; PSEUDOMONAS; ESCHERICHIA COLI; HUMAN; MOUSE; EPIDERMOID CARCINOMA; IMMUNOTHERAPY

Concept Codes:

*18506	Integumentary System-Pathology
*22018	Pharmacology-Immunological Processes and Allergy
*22020	Pharmacology-Integumentary System, Dental and Oral Biology
*24003	Neoplasms and Neoplastic Agents-Immunology
*24008	Neoplasms and Neoplastic Agents-Therapeutic Agents; Therapy
*34508	Immunology and Immunochemistry-Immunopathology, Tissue Immunology
10054	Biochemical Methods-Proteins, Peptides and Amino Acids
10056	Biochemical Methods-Lipids
10058	Biochemical Methods-Carbohydrates
10064	Biochemical Studies-Proteins, Peptides and Amino Acids
10066	Biochemical Studies-Lipids
10068	Biochemical Studies-Carbohydrates
10506	Biophysics-Molecular Properties and Macromolecules
11107	Anatomy and Histology, General and Comparative-Regeneration and Transplantation (1971-)
12100	Movement (1971-)
12512	Pathology, General and Miscellaneous-Therapy (1971-)
13004	Metabolism-Carbohydrates
13006	Metabolism-Lipids
13012	Metabolism-Proteins, Peptides and Amino Acids
15002	Blood, Blood-Forming Organs and Body Fluids-Blood and Lymph Studies
22003	Pharmacology-Drug Metabolism; Metabolic Stimulators
22005	Pharmacology-Clinical Pharmacology (1972-)
22501	Toxicology-General; Methods and Experimental
31000	Physiology and Biochemistry of Bacteria
31500	Genetics of Bacteria and Viruses

Biosystematic Codes:

06508	Pseudomonadaceae (1992-)
06702	Enterobacteriaceae (1992-)
86215	Hominidae
86375	Muridae

Super Taxa:

Microorganisms; Bacteria; Eubacteria; Animals; Chordates; Vertebrates; Mammals; Primates; Humans; Nonhuman Vertebrates; Nonhuman Mammals; Rodents

19/9/7 (Item 7 from file: 5)
DIALOG(R)File 5:BIOSIS PREVIEWS(R)

11121816 BIOSIS Number: 97321816
Pseudomonas *exotoxin* A mutants: Replacement of surface-exposed residues in *domain* *III* with cysteine residues that can be modified with polyethylene glycol in a site-specific manner
Benhar I; Wang Q-C; Fitzgerald D; Pastan I
Lab. Mol. Biol., Div. Cancer Biol., Diagnosis Cent., Natl. Cancer Inst., Natl. Inst. Health, Bethesda, MD 20892, USA
Journal of Biological Chemistry 269 (18). 1994. 13398-13404.
Full Journal Title: Journal of Biological Chemistry
ISSN: 0021-9258
Language: ENGLISH
Print Number: Biological Abstracts Vol. 098 Iss. 002 Ref. 028328
Pseudomonas *exotoxin* A (PE) is composed of three structural and functional domains. Domain Ia is responsible for cell recognition, domain II for translocation of PE across the cell membrane, and *domain* *III* for ADP-ribosylation of elongation factor 2. To investigate the role of the amino acids exposed on the surface of *domain* *III*, we replaced 15 of these, generating 29 different mutants at positions 412, 416, 418, 490, 513, 516, 522, 551, 576, 590, 599, 604, 606, 607 and 608. All but one mutant retained substantial ADP-ribosylation and cytotoxic activities. Modification of proteins with monomethoxypolyethylene glycol (mPEG) prolongs their circulation in the blood stream and reduces their immunogenicity. Unlike PEGylated enzymes acting on small molecule substrates, PEGylated toxins may lose those functions that are based on macromolecular interactions. Therefore, we selectively PEGylated mutant PEs at positions 490, 513, 516, 522, 604, and 606. Most PEs modified by a 5-kDa mPEG via a disulfide or a thioether bond retained high cytotoxic activity. However, when a 20-kDa mPEG was used there was a decrease in cytotoxic activity with the disulfide-bonded molecules being more active. Positions 522 and 604 are good sites for PEGylation, but 490 is not. We also found that PEGylation of PE 522C prolonged its in vivo circulation time in mice.
Descriptors/Keywords: RESEARCH ARTICLE; PSEUDOMONAS AERUGINOSA; MOUSE; LIPOPOLYSACCHARIDE; INFECTION
Concept Codes:
*10506 Biophysics-Molecular Properties and Macromolecules
*22501 Toxicology-General; Methods and Experimental
*31000 Physiology and Biochemistry of Bacteria
*36002 Medical and Clinical Microbiology-Bacteriology
10066 Biochemical Studies-Lipids
10068 Biochemical Studies-Carbohydrates
Biosystematic Codes:
06508 Pseudomonadaceae (1992-)
86375 Muridae
Super Taxa:
Microorganisms; Bacteria; Eubacteria; Animals; Chordates; Vertebrates; Nonhuman Vertebrates; Mammals; Nonhuman Mammals; Rodents

19/9/20 (Item 20 from file: 5)

DIALOG(R)File 5:BIOSIS PREVIEWS(R)

5967461 BIOSIS Number: 84100026
FUNCTIONAL DOMAINS OF *PSEUDOMONAS* *EXOTOXIN* IDENTIFIED BY DELETION ANALYSIS OF THE GENE EXPRESSED IN ESCHERICHIA-COLI
HWANG J; FITZGERALD D J; ADHYA S; PASTAN I
LAB. MOLECULAR BIOL., DIV. CANCER BIOL. DIAGNOSIS, NATL. CANCER INST., NATL. INST. HEALTH, BETHESDA, MD 20892.
CELL 48 (1). 1987. 129-136. CODEN: CELLB
Full Journal Title: Cell
Language: ENGLISH

Pseudomonas *exotoxin* A is a single chain toxin with three structural domains that inhibits protein synthesis in eukaryotic cells by catalyzing ADP ribosylation of elongation factor 2. To study the function of these domains, we deleted different portions of the PE structural gene and expressed these constructs in E. coli using an inducible T7 promoter. These studies indicate that structural domain Ia is required for cell recognition, that structural domain II is required to translocate the toxin across a cellular membrane, and that structural *domain* *III* and a portion of domain Ib are required for ADP ribosylation activity. Toxin lacking domain Ia is about 100-fold less toxic to mice than intact PE and should be a useful molecule for the construction of immunotoxins.
Descriptors/Keywords: MOUSE IMMUNOTOXIN CANCER THERAPY PROTEIN SYNTHESIS CELL MEMBRANE RECOGNITION GENETIC ENGINEERING
Concept Codes:
*02502 Cytology and Cytochemistry-General
*10300 Replication, Transcription, Translation
*10508 Biophysics-Membrane Phenomena
*13012 Metabolism-Proteins, Peptides and Amino Acids
*13014 Metabolism-Nucleic Acids, Purines and Pyrimidines
*22002 Pharmacology-General
*22501 Toxicology-General; Methods and Experimental
*24008 Neoplasms and Neoplastic Agents-Therapeutic Agents; Therapy
*30500 Morphology and Cytology of Bacteria
*31500 Genetics of Bacteria and Viruses
10052 Biochemical Methods-Nucleic Acids, Purines and Pyrimidines
10054 Biochemical Methods-Proteins, Peptides and Amino Acids
10060 Biochemical Studies-General
10062 Biochemical Studies-Nucleic Acids, Purines and Pyrimidines
10064 Biochemical Studies-Proteins, Peptides and Amino Acids
10504 Biophysics-General Biophysical Techniques
Biosystematic Codes:
04716 Pseudomonadaceae (1979-)
04810 Enterobacteriaceae (1979-)
86375 Muridae
Super Taxa:
Microorganisms; Bacteria; Animals; Chordates; Vertebrates; Nonhuman Vertebrates; Mammals; Nonhuman Mammals; Rodents

19/9/21 (Item 1 from file: 73)
DIALOG(R)File 73:EMBASE

9282101 EMBASE No: 94229859
B3(Fab)-PE38(M): A recombinant immunotoxin in which a mutant form of *Pseudomonas* *exotoxin* is fused to the Fab fragment of monoclonal

antibody B3

Choe M.; Webber K.O.; Pastan I.
Laboratory of Molecular Biology, National Cancer Institute, NIH, 9000 Rockville Pike, Bethesda, MD 20892 USA

CANCER RES. (USA) , 1994, 54/13 (3460-3467) CODEN: CNREA ISSN: 0008-5472
LANGUAGES: English SUMMARY LANGUAGES: English
SUBFILES: 016; 026

Recombinant immunotoxins were made by fusing the Fab domain of monoclonal antibody (MAb) B3 to PE38(M), a truncated mutant form of *Pseudomonas* *exotoxin* (PE). The recombinant toxins were made in Escherichia coli by fusing genes encoding the antibody domains to a gene encoding the mutant form of PE. MAb B3 binds to a carbohydrate antigen found on many kinds of carcinomas. Immunotoxins in which MAb B3 has been chemically coupled to recombinant forms of PE have been shown to be very active cytotoxic agents. PE has also been targeted to tumor cells by replacing the cell-binding domain of PE (domain I) with a single-chain antibody to make a single-chain immunotoxin. In the current study, PE38(M), a mutant form of PE, with a deletion of the cell- binding domain (amino acids 1-252) as well as mutations in *domain* *III* and some nonessential sequences in domain Ib (amino acids 365-380), was fused to the light chain of MAb B3. This protein was renatured in the presence of the Fd fragment of MAb B3 to produce a Fab-toxin fusion protein. Alternatively, the Fd fragment of MAb B3 was fused to PE38(M) and combined with the light chain. Both types of B3(Fab)-PE38(M) were just as active on target cells as previously described single-chain immunotoxins. Furthermore, the B3(Fab)- PE38(M) produced complete remissions of human tumor xenografts growing in nude mice. B3(Fab)-PE38(M) has two advantages over single-chain immunotoxins. One is that the yield of recombinant Fab-toxin is very high, with 10-22% of the starting protein recovered as cytotoxically active immunotoxin after chromatographic purification. The second is that the B3(Fab)-PE38(M) has a much longer survival in the circulation of mice with a t(one-halfbeta) of similar5 h.

EMTAGS:
Therapy 0160; Cancer 0306; Heredity 0137; Mammal 0738; Human 0888; Nonhuman 0777; Mouse 0727; Priority journal 0007; Article 0060
DRUG DESCRIPTORS:
*immunotoxin--pharmacology--pd; **pseudomonas* *exotoxin*--endogenous compound--ec; *monoclonal antibody--pharmacology--pd; *immunoglobulin f(ab) fragment--endogenous compound--ec; *hybrid protein
unclassified drug
MEDICAL DESCRIPTORS:
*cancer immunotherapy
cancer regression; cytotoxicity; protein purification; mutation; antineoplastic activity; human; nonhuman; mouse; priority journal; article

DRUG TERMS (UNCONTROLLED): monoclonal antibody b3--pharmacology--pd
EMCLAS DRUG CODES:
03700000000

19/9/26 (Item 1 from file: 357)
DIALOG(R)File 357:Derwent Biotechnology Abs

177110 DBA Accession No.: 95-03931
Design of a genetic immunotoxin to eliminate toxin immunogenicity -

Pseudomonas immunotoxin and Fab fusion protein expression in HIV virus-1-infected Jurkat cell culture, for application in gene therapy by genetic immunization

AUTHOR: Chen S Y; Zani C; Khouri Y; +Marasco W A
CORPORATE AFFILIATE: Dana-Farber-Cancer-Inst. Harvard-Med.Sch.
CORPORATE SOURCE: Department of Medicine, Division of Human Retrovirology, Dana-Farber Cancer Institute, Harvard Medical School, 44 Binney Street, Boston, MA 02115, USA.

JOURNAL: Gene Ther. (2, 2, 116-23) 1995
ISSN: 0969-7128 CODEN: 4352W
LANGUAGE: English

Order

ABSTRACT: A genetic form of immunotoxin (*Pseudomonas* *exotoxin* A (PEA)) was designed to eliminate toxin immunogenicity by replacing the toxin protein moiety with weakly immunogenic or nonimmunogenic plasmid DNA. F105Fd and human protamine DNA fragments were cloned into plasmid pCMV-Fab105 (containing Fab against gp120) and the resulting bicistronic mammalian expression vector (plasmid pCMV-Fab105-protamine) contained an expression cassette for the Fd105-protamine fusion protein and another cassette for the kappa chain of F105, this was used as a gene carrier. To construct the toxin expression plasmid pCMV-PEAIbIII, an upstream primer corresponding to amino acids 384-389 of PEA, and the downstream primer P2 were used to amplify the partial domain Ib and *domain* *III*. The amplified *domain* *III* or *domain* *III* and partial domain Ib DNA sequence of PEA were cloned into a mammalian expression vector plasmid pRc/CMV under control of CMV and T7 promoter, respectively. The complexes were specifically transferred into HIV virus-1-infected Jurkat cells by receptor-mediated endocytosis, resulting in selective killing of the target cells. (35 ref)

DESCRIPTORS: Pseudomonas immunotoxin, Fab fusion protein expression in HIV virus-1-infected Jurkat cell culture, plasmid pCMV-Fab105-protamine, plasmid pCMV-PEAIbIII, appl. gene therapy, genetic immunization bacterium toxin cloning antibody mammal animal human leukemia tumor leuko virus retro virus vector (Vol.14, No.7)
SECTION: PHARMACEUTICALS-Clinical Genetic Techniques; GENETIC ENGINEERING AND FERMENTATION-Nucleic Acid Technology; CELL CULTURE-Animal Cell Culture (D7,A1,J1)

19/9/29 (Item 4 from file: 357)
DIALOG(R)File 357:Derwent Biotechnology Abs

122196 DBA Accession No.: 91-09838 PATENT
Target-specific, cytostatic, Pseudomonas recombinant exotoxin - obtained by mutagenesis of the gene to give a protein altered in *domain* *III* at the carboxyl terminus; insertion of recognition molecule for selective killing of target cells

PATENT ASSIGNEE: Nat.Inst.Health-Bethesda 1990
PATENT NUMBER: US 7459635 PATENT DATE: 900515 WPI ACCESSION NO.: 91-140561 (9119)
PRIORITY APPLIC. NO.: US 459635 APPLIC. DATE: 900102
NATIONAL APPLIC. NO.: US 163429 APPLIC. DATE: 900102
LANGUAGE: English

ABSTRACT: A cytostatic, recombinant *Pseudomonas* *exotoxin* (rPE) is disclosed which has a recognition molecule inserted at least in *domain* *III* at the carboxyl terminus of the PE for selective killing of target cells recognized by the recognition molecule. The rPE does not exhibit cytotoxicity to cells not recognized by the recognition

molecule. Also disclosed is a rPE with modified cytostatic sequences with increased cell killing activity. The rPE molecules are used to prepare target-specific toxins with high cytotoxicity. (33pp)
DESCRIPTORS: Pseudomonas sp. exotoxin gene mutagenesis, insertion of recognition sequence for targeted cell killing, cytostatic bacterium toxin
SECTION: Pharmaceuticals-Other; Microbiology-Genetics (D5,A1)

19/9/30 (Item 5 from file: 357)
DIALOG(R)File 357:Derwent Biotechnology Abs

117388 DBA Accession No.: 91-05030
New cytotoxic agents created by fusion of Pseudomonas toxin and cell targeting molecules - Pseudomonas aeruginosa exotoxin gene cloning and fusion protein preparation with interleukin, CD4, transforming growth factor-alpha, antibody variable region; chimeric toxin (conference paper)
AUTHOR: Pastan I; Lorberboum-Galski; Ogata M; Chaudhary V; FitzGerald D
CORPORATE SOURCE: (Pub.Address) IRL Press at Oxford University Press, Walton Street, Oxford OX2 6DP, UK.
JOURNAL: ICSU Short Rep. (10, 131) 1990
CODEN: 9999Y
LANGUAGE: English
ABSTRACT: A series of point mutations in the *Pseudomonas* *exotoxin* (PE) gene (encoding a 66 kDa protein from Pseudomonas aeruginosa) was created and expressed in Escherichia coli to study the function of the PE gene. Mutations at Lys-57 abolished cell binding. Mutations at Arg-276 or Arg-279 decreased cytotoxicity and prevented processing and translocation of *domain* *III* (responsible for ADP ribosylation of elongation factor-2) into the cytosol. A sequence near the C-terminus of *domain* *III* was identified, which was also required for the cytotoxic activity of PE. Domain I (responsible for cell binding) of PE was replaced by various growth factors and lymphokines (transforming growth factor-alpha, interleukin-2, interleukin-4, interleukin-6, CD4 and variable regions of antibodies) to create chimeric cytotoxic molecules. The properties and biological effects of some of these chimeric molecules were discussed. (3 ref)
DESCRIPTORS: Pseudomonas aeruginosa exotoxin gene cloning, fusion protein prep. with interleukin-2, interleukin-4, interleukin-6, CD4, transforming growth factor-alpha, antibody variable region, expression in Escherichia coli, protein engineering, chimeric toxin prep. bacterium lymphokine transformation
SECTION: Pharmaceuticals-Other; Microbiology-Genetics (D5,A1)

19/9/31 (Item 6 from file: 357)
DIALOG(R)File 357:Derwent Biotechnology Abs

095183 DBA Accession No.: 89-13174
Pseudomonas *exotoxin*: chimeric toxins - production and application, review
AUTHOR: Pastan I; Fitzgerald D
CORPORATE SOURCE: Laboratory of Molecular Biology, National Cancer Institute, Division of Cancer, Biology and Diagnosis, National Institutes of Health, Bethesda, Maryland 20892, USA.

JOURNAL: J.Biol.Chem. (264, 26, 15157-60) 1989
CODEN: JBCHA3
LANGUAGE: English
MF
ABSTRACT: The production of chimeric toxins using Pseudomonas sp. exotoxin is reviewed. *Pseudomonas* *exotoxin* binds to and enters cells by receptor-mediated endocytosis. Within the cell it requires exposure to low pH to enable it to translocate to the cell cytoplasm where it inhibits protein synthesis by ADP-ribosylating elongation factor 2. The toxin has 3 main structural domains. The functions of each domain were confirmed by mutagenesis to be cell binding (domain Ia), translocation (domain II) and ADP-ribosylation (*domain* *III*). Key amino acids have been identified within each domain that are required for the function of the toxin. Chimeric toxins were made originally by using chemical crosslinking reagents to couple *Pseudomonas* *exotoxin* to cell-binding proteins. More recently, *Pseudomonas* *exotoxin*-related chimeric toxins have been made by gene fusion technology, involving deletion of part of the toxin gene, and replacement with DNA coding for e.g. peptide hormones or growth factors. These chimeric toxins may be useful clinically for treating various diseases and experimentally for understanding receptor function. (58 ref)
DESCRIPTORS: Pseudomonas spp. chimer

4/9/3 (Item 3 from file: 5)
DIALOG(R)File 5:BIOSIS PREVIEWS(R)

10120258 BIOSIS Number: 95120258
CHARACTERIZATION OF SINGLE-CHAIN ANTIBODY SFV-TOXIN FUSION PROTEINS PRODUCED IN-VITRO IN RABBIT RETICULOCYTE LYSATE
NICHOLLS P J; JOHNSON V G; ANDREW S M; HOOGENBOOM H R; RAUS J C M; YOULE R J
BIOCHEMISTRY SECTION, SURGICAL NEUROLOGY BRANCH, NATIONAL INSTITUTE NEUROLOGICAL DISEASES STROKE, NATIONAL INSTITUTES HEALTH, BETHESDA, MD 20892, USA.
J BIOL CHEM 268 (7). 1993. 5302-5308. CODEN: JBCHA
Full Journal Title: Journal of Biological Chemistry
Language: ENGLISH
Chimeric proteins consisting of a fusion between binding-deficient mutants of diphtheria toxin (DT) or Pseudomonas exotoxin A (PE) and a single-chain antibody (E6 sFv) against the human *transferrin* receptor (TfnR) were expressed in a rabbit reticulocyte lysate system. Molecules utilizing PE40 (the carboxyl terminus 40 kDa of PE, lacking the binding domain) exhibited significant E6 sFv-mediated, cell type-specific cytotoxicity (IC50 1 .times. 10-10 M) against a human erythroleukemia-derived cell line, K562. In contrast, a *fusion* *protein* between the same sFv and a DT mutant, DTMI (containing two amino acid substitutions in the binding domain [S(508)F, S(525)F]) was not significantly cytotoxic, despite being enzymatically active. A tripartite protein in the form NH2-DTM1-E6 sFv-PE40-COOH exhibited cytotoxicity comparable to that of the PE40-sFv fusion (IC50 1 .times. 10-10 M), suggesting that the deficit in activity of DTM1-sFv is not a function of misfolding of the sFv moiety or of a reduced ability to bind TfnR. In contrast to DTM1-E6 sFv, a *fusion* *protein* between a second DT mutant, CRM 107 [S(525)F], and the E6 sFv was specifically cytotoxic (IC50 1 .times. 10-9 M), and toxicity could be blocked by addition of excess E6 antibody. The cell-free in vitro expression system we describe is rapid and may be used to express functional toxin-sFv fusion proteins. No protein refolding procedures are required, and the technique may be used to express proteins which, due to restrictions imposed on manipulation of toxin-encoding genes in Escherichia coli, could not be produced by more conventional methods.
Descriptors/Keywords: PSEUDOMONAS ESCHERICHIA-COLI DIPHTHERIA TOXIN EXOTOXIN A TOXIN-ENCODING GENE BIOLOGICAL CHEMISTRY IMMUNOTOXIN
Concept Codes:
*02506 Cytology and Cytochemistry-Animal
*10064 Biochemical Studies-Proteins, Peptides and Amino Acids
*15008 Blood, Blood-Forming Organs and Body Fluids-Lymphatic Tissue and Reticuloendothelial System
*22018 Pharmacology-Immunological Processes and Allergy
*22501 Toxicology-General; Methods and Experimental
*31000 Physiology and Biochemistry of Bacteria
*31500 Genetics of Bacteria and Viruses
*34504 Immunology and Immunochemistry-Bacterial, Viral and Fungal
*34508 Immunology and Immunochemistry-Immunopathology, Tissue Immunology
*36002 Medical and Clinical Microbiology-Bacteriology
10068 Biochemical Studies-Carbohydrates
32500 Tissue Culture, Apparatus, Methods and Media
Biosystematic Codes:
06508 Pseudomonadaceae (1992-)

06702 Enterobacteriaceae (1992-)
08890 Irregular Nonsporing Gram-Positive Rods (1992-)
86040 Leporidae
Super Taxa:
Microorganisms; Bacteria; Eubacteria; Animals; Chordates; Vertebrates; Nonhuman Vertebrates; Mammals; Nonhuman Mammals; Lagomorphs

4/9/6 (Item 6 from file: 5)
DIALOG(R)File 5:BIOSIS PREVIEWS(R)

9500212 BIOSIS Number: 94005212
HUMANIZATION OF IMMUNOTOXINS
RYBAK S M; HOOGENBOOM H R; MEADE H M; RAUS J C M; SCHWARTZ D; YOULE R J
BIOCHEMISTRY SECTION, SURGICAL NEUROLOGY BRANCH, NATIONAL INSTITUTE NEUROLOGICAL DISORDERS STROKE, NATIONAL INSTITUTES HEALTH, BETHESDA, MD. 20896.
PROC NATL ACAD SCI U S A 89 (8). 1992. 3165-3169. CODEN: PNASA
Full Journal Title: Proceedings of the National Academy of Sciences of the United States of America
Language: ENGLISH
The construction and expression of a chimeric gene encoding a mouse/human antibody to the human *transferrin* receptor fused to the gene for angiogenin, a human homolog of pancreatic RNase, are described. F(ab')2-like antibody-enzyme fusions were prepared by linking the gene for human angiogenin to a chimeric anti-*transferrin* receptor heavy chain gene. The antibody-enzyme fusion gene was introduced into a transfectoma that secretes the chimeric light chain of the same antibody, and cell lines were cloned that synthesize and secrete the antibody-enzyme *fusion* *protein* of the expected size at a concentration of 1-5 ng/ml. Culture supernatants from clones secreting the *fusion* *protein* caused inhibition of growth and protein synthesis of K562 cells that express the human *transferrin* receptor but not toward a non-human-derived cell line that lacks this receptor. Whereas excess antibody to the same receptor did not itself inhibit protein synthesis, it was able to completely prevent the protein synthesis inhibition caused by the *fusion* *protein*. These results indicate that the cytotoxicity is due to a *transferrin* receptor-mediated mechanism involving the angiogenin portion of the *fusion* *protein* and demonstrate the feasibility of constructing recombinant antibody-RNase molecules capable of killing tumor cells bearing the *transferrin* receptor. The significance of the acquired cytotoxicity of a mouse/human chimeric antibody linked to a human protein may bear importantly in human therapeutic strategies that use mouse antibody linked to toxins from plants or bacteria to target tumor cells. It is expected that the humanization of immunotoxins will lead to less toxicity and immunogenicity than currently available reagents.
Descriptors/Keywords: MOUSE-HUMAN ANTIBODY RNASE ANGIOGENIN CHIMERIC ANTIBODY CANCER IMMUNOTHERAPY
Concept Codes:
*03506 Genetics and Cytogenetics-Animal
*03508 Genetics and Cytogenetics-Human
*22018 Pharmacology-Immunological Processes and Allergy
*24008 Neoplasms and Neoplastic Agents-Therapeutic Agents; Therapy
*34502 Immunology and Immunochemistry-General; Methods
10064 Biochemical Studies-Proteins, Peptides and Amino Acids
10808 Enzymes-Physiological Studies
12512 Pathology, General and Miscellaneous-Therapy (1971-)

Biosystematic Codes:
86215 Hominidae
86375 Muridae
Super Taxa:
Animals; Chordates; Vertebrates; Mammals; Primates; Humans; Nonhuman Vertebrates; Nonhuman Mammals; Rodents

4/9/25 (Item 1 from file: 399)
DIALOG(R)File 399:CA SEARCH(R)

118094318 CA: 118(11)94318q PATENT
Selective cytotoxic reagents
INVENTOR(AUTHOR): Rybak, Susanna M.; Youle, Richard J.
LOCATION: USA
ASSIGNEE: United States Dept. of Health and Human Services
PATENT: U.S. Pat. Appl. ; US 779195 A0 DATE: 921215
APPLICATION: US 779195 (911022)
PAGES: 51 pp. Avail. NTIS Order No. PAT-APPL-7-779,195. CODEN: XAXXAV
LANGUAGE: English
SECTION:
CA201006 Pharmacology
CA263XXX Pharmaceuticals
IDENTIFIERS: cytotoxic reagent RNase targeting conjugate, angiogenin fusion protein antibody antitumor, transferrin receptor antibody fusion protein angiogenin
DESCRIPTORS:
Cell...
agent targeting, toxic mammalian protein conjugate or fusion protein with
Neoplasm inhibitors...
chimeric anti-transferrin receptor antibody-angiogenin conjugates or RNase-transferrin conjugates as
Receptors,transferrin... Transferrins,receptors...
chimeric antibody to, conjugates with human angiogenin, as neoplasm inhibitors
Gene,animal...
for angiogenin, of human, cloning of, in prepn. of anti-transferrin receptor antibody fusion protein as neoplasm inhibitor
Animal growth regulators,angiogenic factors...
fusion proteins with chimeric antibodies, as cytotoxic reagents
Antibodies...
to cell surface marker, conjugated or fused with toxic mammalian protein, as cytotoxic reagent
Antibodies,monoclonal...
to transferrin receptor of human, conjugates with human angiogenin, as neoplasm inhibitors
Proteins,specific or class, conjugates... Proteins,specific or class, fusion products...
toxic, of mammal, with targeting agent, as cytotoxic reagent
Mammal...
toxic protein of, conjugated or fused with targeting agent, as cytotoxic reagent
Cytotoxic agents...
toxic protein of mammal conjugated or fused with targeting agent
Transferrins,conjugates...
with RNase, as neoplasm inhibitors

CAS REGISTRY NUMBERS:
9001-99-4D fusion proteins with chimeric antibodies, as cytotoxic reagents
?ds

Set	Items	Description
S1	38233	TRANSFERRIN
S2	18958	FUSION(W)PROTEIN
S3	55	S1 AND S2
S4	27	RD (unique items)

?s s1 and protamine

	38233	S1
	11143	PROTAMINE
S5	54	S1 AND PROTAMINE

?s s5 and fusion

	54	S5
	189285	FUSION
S6	3	S5 AND FUSION

?rd

...completed examining records

S7	1	RD (unique items)

?t s7/9/1

7/9/1 (Item 1 from file: 5)
DIALOG(R)File 5:BIOSIS PREVIEWS(R)

11202298 BIOSIS Number: 97402298
Localization of mRNAs by in situ hybridization to the residual body at stages IX-X of the cycle of the rat seminiferous epithelium: Fact or artefact?
Millar M R; Sharpe R M; Maguire S M; Gaughan J; West A P; Saunders P T K
MRC Reproductive Biol. Unit, 37 Chalmers St., Edinburgh EH3 9EW, UK
International Journal of Andrology 17 (3). 1994. 149-160.
Full Journal Title: International Journal of Andrology
ISSN: 0105-6263
Language: ENGLISH
Print Number: Biological Abstracts Vol. 098 Iss. 006 Ref. 073110
Several recent articles have reported localization of specific mRNAs in the rat testis to stage IX and X seminiferous tubules using in-situ hybridization. In all cases the expression was located basally in the tubules and appeared as discrete round clusters of grains close to the lamina propria. The localization was interpreted as being in Sertoli cells or leptotene spermatocytes. In this study we demonstrate that this pattern is most probably due to artifactual binding of probes to the residual body (RB). In the present study testicular tissue, perfusion-fixed with Bouin's and embedded in paraffin, was used, as this resulted in excellent morphological preservation such that RBs within tubules at stages VIII-X were clearly distinguishable. RNA content of the RBs was demonstrated at stages VIII-X using methyl green pyronine staining, and could be eliminated by pretreatment with PNAse or trichloroacetic acid. Localization of mRNAs for 11 seminiferous tubule proteins was assessed using 35S-labelled and digoxigenin-labelled riboprobes (activin receptor-II, alpha-inhibin, *transferrin* , androgen-binding protein (ABP), cyclic protein-2 (CP-2),

CREM, sulphated glycoproteins 1 and 2 (SGP-1 and SGP-2), transition protein 2 (TP-2) and cystatin-C), and digoxigenin-labelled oligonucleotide probes (transition protein-1 (TP-1), TP-2 and *protamine*-1). All of these probes showed localization to the correct cell type(s) within the seminiferous epithelium. In addition, six antisense riboprobes (activin receptor-II, CREM, SGP-2, CP-2, cystatin C and alpha-inhibin) showed hybridization to basally located residual bodies in tubules at stages IX-X on one or more occasions, whereas residual bodies around the edge of the lumen (stage VIII) or in transit through the seminiferous epithelium showed no hybridization; sense probes showed no localization to residual bodies. A common feature of the probes which localized to the basal RBs was that they had been prepared using cDNA cloned into Bluescript SK-vector such that the antisense strand was generated from the T7 polymerase promotor. A cRNA prepared using T7 polymerase and Bluescript vector alone and a GC-rich 27mer oligonucleotide corresponding to the region of the multiple cloning site of Bluescript adjacent to the T7 site both localized uniquely to basal RB. It is concluded that the hybridization seen within RBs is probably a subtle artefact unique to PBs undergoing dissolution following *fusion* with Sertoli cell lysosomes, and may reflect nonspecific hybridization to GC-rich fragments of RNA.

Descriptors/Keywords: RESEARCH ARTICLE; MESSENGER RNA; ACTIVIN RECEPTOR; ALPHA-INHIBIN; CYCLIC PROTEIN 2; TRANSITION PROTEIN-1; TRANSITION PROTEIN-2; TESTIS; ANDROLOGY

Concept Codes:

*02506 Cytology and Cytochemistry-Animal
*10062 Biochemical Studies-Nucleic Acids, Purines and Pyrimidines
*16502 Reproductive System-Anatomy
*16504 Reproductive System-Physiology and Biochemistry
*17006 Endocrine System-Gonads and Placenta
*25508 Developmental Biology-Embryology-Morphogenesis, General

Biosystematic Codes:

86375 Muridae

Super Taxa:

Animals; Chordates; Vertebrates; Nonhuman Vertebrates; Mammals; Nonhuman Mammals; Rodents

S1	61910	DNA(W)BINDING
S2	341364	(GENE OR CDNA) AND SEQUENCE
S3	18171	S1 AND S2
S4	24598	FOS OR JUN
S5	1033	S3 AND S4
S6	589	S5 NOT PY=1993:1995

6/9/6 (Item 6 from file: 5)
DIALOG(R)File 5:BIOSIS PREVIEWS(R)

9602855 BIOSIS Number: 94107855
REDOX ACTIVATION OF *FOS*-*JUN* *DNA* *BINDING* ACTIVITY IS MEDIATED BY A DNA REPAIR ENZYME
XANTHOUDAKIS S; MIAO G; WANG F; PAN Y-C E; CURRAN T
DEP. MOLECULAR ONCOLOGY VIROLOGY, ROCHE INSTITUTE MOLECULAR BIOLOGY, COLUMBIA UNIVERSITY, NEW YORK, N.Y. 10037.
EMBO (EUR MOL BIOL ORGAN) J 11 (9). 1992. 3323-3335. CODEN: EMJOD
Full Journal Title: EMBO (European Molecular Biology Organization) Journal
Language: ENGLISH
The *DNA* *binding* activity of *Fos* and *Jun* is regulated in vitro by a post-translational mechanism involving reduction-oxidation. Redox regulation occurs through a conserved cysteine residue located in the *DNA* *binding* domain of *Fos* and *Jun*. Reduction of this residue by chemical reducing agents or by a ubiquitous nuclear redox factor (Ref-1) recently purified from Hela cells, stimulates AP-1 *DNA* *binding* activity in vitro, whereas oxidation or chemical modification of the cysteine has an inhibitory effect on *DNA* *binding* activity. Here we demonstrate that the protein product of the ref-1 *gene* stimulates the *DNA* *binding* activity of *Fos*-*Jun* heterodimers, *Jun*-*Jun* homodimers and Hela cell AP-1 proteins as well as that of several other transcription factors including NF-.kappa.B, Myb and members of the ATF/CREB family. Furthermore, immunodepletion analysis indicates that Ref-1 is the major AP-1 redox activity in Hela nuclear extracts. Interestingly, Ref-1 is a bifunctional protein; it also possesses an apurinic/apryimidinic (AP) endonuclease DNA repair activity. However, the redox and DNA repair activities of Ref-1 can, in part, be distinguished biochemically. This study suggests a novel link between transcription factor regulation, oxidative signalling and DNA repair processes in higher eukarocytes.
Descriptors/Keywords: HUMAN COMPLEMENTARY DNA NUCLEAR REDOX FACTOR ENDONUCLEASE HELA CELLS POST TRANSLATIONAL MECHANISM MOLECULAR *SEQUENCE* DATA NUCLEOTIDE *SEQUENCE* AMINO ACID *SEQUENCE*
Concept Codes:
*02508 Cytology and Cytochemistry-Human
*03508 Genetics and Cytogenetics-Human
*10300 Replication, Transcription, Translation
*10808 Enzymes-Physiological Studies
*13014 Metabolism-Nucleic Acids, Purines and Pyrimidines
10062 Biochemical Studies-Nucleic Acids, Purines and Pyrimidines
10064 Biochemical Studies-Proteins, Peptides and Amino Acids
10506 Biophysics-Molecular Properties and Macromolecules
Biosystematic Codes:
86215 Hominidae
Super Taxa:
Animals; Chordates; Vertebrates; Mammals; Primates; Humans

6/9/18 (Item 18 from file: 5)
DIALOG(R)File 5:BIOSIS PREVIEWS(R)

9499605 BIOSIS Number: 94004605
FOS AND *JUN* REPRESS TRANSCRIPTIONAL ACTIVATION BY MYOGENIN AND MYOD THE AMINO TERMINUS OF *JUN* CAN MEDIATE REPRESSION

LI L; CHAMBARD J-C; KARIN M; OLSON E N
DEP. BIOCHEMISTRY MOLECULAR BIOLOGY, UNIVERSITY M.D. ANDERSON CANCER CENTER, HOUSTON, TEX. 77030, USA.
GENES DEV 6 (4). 1992. 676-689. CODEN: GEDEE
Full Journal Title: Genes & Development
Language: ENGLISH

Myogenin and MyoD belong to a family of muscle-specific helix-loop-helix (HLH) proteins that have the potential to activate muscle-specific genes in nonmyogenic cells. Peptide growth factors can block the ability of myogenin and MyoD to activate their target genes. Here, we show that the growth factor-inducible proto-oncogenes c-*fos*, c-*jun* , and junB mimic the effects of exogenous growth factors and suppress trans-activation of the muscle creatine kinase (MCK) enhancer by myogenin and MyoD. In contrast, JunD, which shares *DNA*-*binding* specificity with JunB and c-*Jun* but is expressed constitutively in muscle cells, is an inefficient inhibitor of the trans-activating capacity of myogenin and MyoD. Transcriptional repression by *Fos* and *Jun* is specific to myogenic HLH proteins and is not observed with the widely expressed HLH protein E47, which recognizes the same DNA *sequence*. Repression of the MCK enhancer by *Fos* and *Jun* is targeted at the myogenin and MyoD DNA recognition *sequence* and can be mediated by the amino terminus of c-*Jun*. Comparison of several myogenin mutants for their responsiveness to *Fos* and *Jun* shows that repression is directed at the basic-HLH region. These results indicate that members of the *Jun* family can be distinguished on the basis of their effects on muscle-specific transcription and suggest there is cross talk between transcription factors that control myogenesis and those involved in cell proliferation.

Descriptors/Keywords: DNA RECOGNITION *SEQUENCE* MUSCLE-SPECIFIC *GENE* HELIX-LOOP-HELIX CREATINE KINASE MYOGENESIS

Concept Codes:
*03506 Genetics and Cytogenetics-Animal
*10062 Biochemical Studies-Nucleic Acids, Purines and Pyrimidines
*10064 Biochemical Studies-Proteins, Peptides and Amino Acids
*10300 Replication, Transcription, Translation
*10506 Biophysics-Molecular Properties and Macromolecules
*10806 Enzymes-Chemical and Physical
*10808 Enzymes-Physiological Studies
*17504 Muscle-Physiology and Biochemistry
*25508 Developmental Biology-Embryology-Morphogenesis, General

6/9/31 (Item 31 from file: 5)
DIALOG(R)File 5:BIOSIS PREVIEWS(R)

8551255 BIOSIS Number: 92016255
FOSB IS A TRANSFORMING *GENE* ENCODING A TRANSCRIPTIONAL ACTIVATOR
SCHUERMANN M; JOOSS K; MUELLER R
INST. MOLEKULARBIOLOGIE TUMORFORSCHUNG, PHILIPPS-UNIV. MARBURG, EMIL-MANNKOPFF-STR. 2, D-3550 MARBURG, W. GER.
ONCOGENE 6 (4). 1991. 567-576. CODEN: ONCNE
Full Journal Title: Oncogene
Language: ENGLISH

The fosB *gene* encodes a nuclear protein that shows a high degree of homology with c-*Fos* in several of the known functionally crucial domains, e.g., the leucine zipper and the *DNA*-*binding* site, but shows considerable divergence in other regions. Here, we report that FosB, when placed under the control of a constitutive promoter, exhibits clear

transforming properties in focus assays using mouse NIH3T3 or rat 208F fibroblasts. The transforming potential of FosB is considerably stronger than that of a corresponding c-*fos* construct and resembles that of viral *fos* genes. Using chimeric *fos* /fosB constructs we show that the C-terminal half of FosB is responsible for these stronger transforming properties, apparently by giving rise to significantly higher levels of protein as compared with the corresponding c-*fos* *sequence* . Surprisingly, substitution of the N-terminus of *Fos* with that of FosB decreases its transforming potential. These differences in the transforming potential are not related to DNA or protein expression, but rather seem to reflect differences in the molecular function(s) encoded in the N-terminal halves of *Fos* and FosB protein. Both, fosB- and v-*fos* transformed cells show increased expression of a number of endogenous genes, including c-*jun* , transin, .alpha.1(III) collagen and tissue plasminogen activator. Transactivation by FosB and v-*fos* of the c-*jun* and .alpha.1(III) collagen *gene* promoters and of a 3 .times. TRE-tk chimeric promoter could be shown in transient CAT assays. v-*FOS*, but not FosB-transformed cells, also show elevated levels of urokinase and plasminogen activator inhibitor mRNAs, pointing to potential differences in the *gene* regulatory properties of the two *Fos* family members.

Descriptors/Keywords: HUMAN MOUSE HELA 208F NIH3T3 CELL LINE MESSENGER RNA DNA UROKINASE PLASMINOGEN ACTIVATOR INHIBITOR

Concept Codes:

*02506	Cytology and Cytochemistry-Animal
*02508	Cytology and Cytochemistry-Human
*03506	Genetics and Cytogenetics-Animal
*03508	Genetics and Cytogenetics-Human
*10062	Biochemical Studies-Nucleic Acids, Purines and Pyrimidines
*10064	Biochemical Studies-Proteins, Peptides and Amino Acids
*10300	Replication, Transcription, Translation
*10806	Enzymes-Chemical and Physical
*15002	Blood, Blood-Forming Organs and Body Fluids-Blood and Lymph Studies

Biosystematic Codes:

86215	Hominidae
86375	Muridae

Super Taxa:

Animals; Chordates; Vertebrates; Mammals; Primates; Humans; Nonhuman Vertebrates; Nonhuman Mammals; Rodents

6/9/34 (Item 34 from file: 5)
DIALOG(R)File 5:BIOSIS PREVIEWS(R)

8185946 BIOSIS Number: 91106946

A NATURALLY OCCURRING TRUNCATED FORM OF FOSB THAT INHIBITS *FOS*-*JUN* TRANSCRIPTIONAL ACTIVITY

NAKABEPPU Y; NATHANS D
HOWARD HUGHES MED. INST., BALTIMORE, MD. 21205.

CELL 64 (4). 1991. 751-760. CODEN: CELLB
Full Journal Title: Cell
Language: ENGLISH

Fos and *Jun* transcription factors are induced by a variety of extracellular signaling agents. We describe here an unusual member of the *Fos* family that is also induced, namely, a truncated form of FosB (.DELTA.FosB) missing the C-terminal 101 amino acids of FosB. .DELTA.FosB retains the dimerization and *DNA*-*binding* activities of FosB but has

lost the ability in transfection assays to activate a promoter with an AP-1 site and to repress the c-*fos* promoter. Rather, .DELTA.FosB inhibits *gene* activation by *Jun* or *Jun* + *Fos* and inhibits repression of the c-*fos* promoter by FosB or c-*Fos* , presumably by competing with full-length *Fos* proteins at the steps of dimerization with *Jun* and binding to DNA. In stimulated cells .DELTA.FosB may act to limit the transcriptional effects of *Fos* and *Jun* proteins.
Descriptors/Keywords: MOUSE *GENE* ACTIVATION *DNA* *BINDING* AMINO ACID *SEQUENCE* NUCLEOTIDE *SEQUENCE* MOLECULAR *SEQUENCE* DATA
Concept Codes:
*02506 Cytology and Cytochemistry-Animal
*03506 Genetics and Cytogenetics-Animal
*10062 Biochemical Studies-Nucleic Acids, Purines and Pyrimidines
*10064 Biochemical Studies-Proteins, Peptides and Amino Acids
*10300 Replication, Transcription, Translation
*10506 Biophysics-Molecular Properties and Macromolecules
13014 Metabolism-Nucleic Acids, Purines and Pyrimidines
Biosystematic Codes:
86375 Muridae
Super Taxa:
Animals; Chordates; Vertebrates; Nonhuman Vertebrates; Mammals; Nonhuman Mammals; Rodents

6/9/48 (Item 48 from file: 5)
DIALOG(R)File 5:BIOSIS PREVIEWS(R)

7709076 BIOSIS Number: 90077076
ONCOGENE V-*JUN* MODULATES DNA REPLICATION
WASYLYK C; SCHNEIKERT J; WASYLYK B
LAB. DE GENETIQUE MOL. DES EUCARYOTES DU CNRS, UNITE 184 DE BIOL. MOL. ET DE GENIE GENETIQUE DE L'INSERM, INST. DE CHIMIE BIOL., FAC. DE MEDECINE, 11 RUE HUMANN, 67085 STRASBOURG CEDEX, FR.
ONCOGENE 5 (7). 1990. 1055-1058. CODEN: ONCNE
Full Journal Title: Oncogene
Language: ENGLISH
Cell transformation leads to alterations in both transcription and DNA replication. Activation of transcription by the expression of a number of transforming oncogenes is mediated by the transcription factor AP1 (Herrlich & Ponta, 1989; Imler & Wasylyk, 1989). AP1 is a composite transcription factor, consisting of members of the *jun* and *fos* *gene* -families. c-*jun* and c-*fos* are progenitors of oncogenes, suggesting that an important transcriptional event in cell transformation is altered activity of AP1, which may arise either indirectly by oncogene expression or directly by structural modification of AP1. We report here that the v-*jun* oncogene and its progenitor c-*jun*, as fusion proteins with the lex-A-repressor *DNA* *binding* domain, can activate DNA replication from the Polyoma virus (Py) origin of replication, linked to the lex-A operator. The transcription-activation region of v-*jun* is required for activation of replication. When excess v-*jun* is expressed in the cell, replication is inhibited or 'squelched'. These results suggest that one consequence of deregulated *jun* activity could be altered DNA replication and that there are similarities in the way v-*jun* activates replication and transcription.
Descriptors/Keywords: RABBIT POLYOMA VIRUS TRANSCRIPTION MOLECULAR *SEQUENCE* DATA NUCLEOTIDE *SEQUENCE*
Concept Codes:

*02506 Cytology and Cytochemistry-Animal
*03506 Genetics and Cytogenetics-Animal
*10062 Biochemical Studies-Nucleic Acids, Purines and Pyrimidines
*10300 Replication, Transcription, Translation
*10506 Biophysics-Molecular Properties and Macromolecules
*13014 Metabolism-Nucleic Acids, Purines and Pyrimidines
*24007 Neoplasms and Neoplastic Agents-Carcinogens and Carcinogenesis
*33506 Virology-Animal Host Viruses
10052 Biochemical Methods-Nucleic Acids, Purines and Pyrimidines
10504 Biophysics-General Biophysical Techniques
Biosystematic Codes:
02226 Papovaviridae (1979-)
86040 Leporidae
Super Taxa:
Microorganisms; Viruses; Animals; Chordates; Vertebrates; Nonhuman Vertebrates; Mammals; Nonhuman Mammals; Lagomorphs

6/9/56 (Item 56 from file: 5)
DIALOG(R)File 5:BIOSIS PREVIEWS(R)

7477247 BIOSIS Number: 89128266
DIRECT CLONING OF LEUCINE ZIPPER PROTEINS *JUN* BINDS COOPERATIVELY TO THE CRE WITH CRE-BP1
MACGREGOR P F; ABATE C; CURRAN T
DEP. MOL. ONCOL. VIROL., ROCHE INST. MOL. BIOL., ROCHE RES. CENT., NUTLEY, NEW JERSEY 07110, USA.
ONCOGENE 5 (4). 1990. 451-458. CODEN: ONCNE
Full Journal Title: Oncogene
Language: ENGLISH
The proto-oncogene products *Fos* and *Jun* form a stable heterodimeric complex that functions in transcriptional regulation by interacting with the DNA *sequence* known as the AP-1 site. Dimer formation occurs through the leucine zipper, a structural motif involving a heptad repeat of leucine residues there is conserved in several *fos*- and *jun*-related genes. We have employed a novel cloning strategy to isolate genes encoding proteins capable of forming complexes with *Jun*. The procedure involves direct screening of a .lambda.gt11 *cDNA* library with with a biotinylated *Jun* polypeptide. One clone isolated in this manner encodes CRE-BP1, a leucine zipper-containing protein that binds to the cyclic AMP response element (CRE) as a homodimer. CRE-BPI also forms heterodimeters with *Jun* but not with *Fos*. *Jun* binds cooperatively to the CRE in association with CRE-BP1. Thus, the *DNA*-*binding* specificity and affinity of *Jun* are modulated by association with *Fos* or with CRE-BP1.
Descriptors/Keywords: RAT FIBROBLASTS CYCLIC AMP RESPONSIVE ELEMENT PROTO-ONCOGENE PROTEIN DIMER FORMATION *DNA* *BINDING* SPECIFICITY GEL SHIFT ASSAY PROTEIN BLOT ANALYSIS COMPLEMENTARY DNA LIBRARY SCREENING
Concept Codes:
*02506 Cytology and Cytochemistry-Animal
*03506 Genetics and Cytogenetics-Animal
*10062 Biochemical Studies-Nucleic Acids, Purines and Pyrimidines
*10064 Biochemical Studies-Proteins, Peptides and Amino Acids
*10506 Biophysics-Molecular Properties and Macromolecules
*24007 Neoplasms and Neoplastic Agents-Carcinogens and Carcinogenesis
*33506 Virology-Animal Host Viruses
10052 Biochemical Methods-Nucleic Acids, Purines and Pyrimidines
10054 Biochemical Methods-Proteins, Peptides and Amino Acids

10504 Biophysics-General Biophysical Techniques
Biosystematic Codes:
86375 Muridae
Super Taxa:
Animals; Chordates; Vertebrates; Nonhuman Vertebrates; Mammals; Nonhuman Mammals; Rodents

6/9/57 (Item 57 from file: 5)
DIALOG(R)File 5:BIOSIS PREVIEWS(R)

7475867 BIOSIS Number: 89126886
A NEW MEMBER OF THE LEUCINE ZIPPER CLASS OF PROTEINS THAT BINDS TO THE HLA DR-ALPHA PROMOTER
LIOU H-C; BOOTHBY M R; FINN P W; DAVIDSON R; NABAVI N; ZELEZNIK-LE N J; TING J P-Y; GLIMCHER L H
DEP. CANCER BIOL., HARVARD SCH. PUBLIC HEALTH, BOSTON, MASS. 02115.
SCIENCE (WASHINGTON D C) 247 (4950). 1990. 1581-1584. CODEN: SCIEA
Full Journal Title: SCIENCE (Washington D C)
Language: ENGLISH
Several mutants derived from transformed human B cell lines are defective in expressing major histocompatibility complex (MHC) class II genes. The failure to express a class II *gene* in at least one such mutant line has been mapped to the MHC class II X box, a conserved transcriptional element in the promoter region. A complementary DNA encoding a *DNA*-*binding* protein (human X box binding protien, hXBP-1) whose target is the human DR.alpha. X box and the 3' flanking region has now been cloned. The complementary DNA encoded a protein with structural similarities to the c-*jun* proto-oncogene product, and its target *sequence* was closely related to the palindromic target *sequence* of c-*jun*. Mutation of the hXBP-1 DNA target *sequence* decreased DR.alpha. promoter activity in vivo. These studies suggest that the hXBP-1 protein acts as a transcription factor in B cells.
Descriptors/Keywords: HUMAN B CELLS MAJOR HISTOCOMPATIBILITY COMPLEX COMPLEMENTARY DNA MOLECULAR *SEQUENCE* DATA NUCLEIC ACID *SEQUENCE* AMINO ACID *SEQUENCE* C-*JUN* PROTO-ONCOGENE TRANSCRIPTION
Concept Codes:
*03508 Genetics and Cytogenetics-Human
*10062 Biochemical Studies-Nucleic Acids, Purines and Pyrimidines
*10064 Biochemical Studies-Proteins, Peptides and Amino Acids
*10300 Replication, Transcription, Translation
*10506 Biophysics-Molecular Properties and Macromolecules
*25508 Developmental Biology-Embryology-Morphogenesis, General
*34508 Immunology and Immunochemistry-Immunopathology, Tissue Immunology
13012 Metabolism-Proteins, Peptides and Amino Acids
13014 Metabolism-Nucleic Acids, Purines and Pyrimidines
Biosystematic Codes:
86215 Hominidae
Super Taxa:
Animals; Chordates; Vertebrates; Mammals; Primates; Humans

6/9/77 (Item 77 from file: 5)
DIALOG(R)File 5:BIOSIS PREVIEWS(R)

7054460 BIOSIS Number: 87114981
THE PRODUCT OF A NOVEL GROWTH FACTOR ACTIVATED *GENE* *FOS* B INTERACTS WITH *JUN* PROTEINS ENHANCING THEIR *DNA* *BINDING* ACTIVITY
ZERIAL M; TOSCHI L; RYSECK R-P; SCHUERMANN M; MUELLER R; BRAVO R
EUROPEAN MOL. BIOL. LAB., POSTFACH 10.2209, MEYERHOFSTRASSE 1, 6900 HEIDELBERG, FRG.
EMBO (EUR MOL BIOL ORGAN) J 8 (3). 1989. 805-814. CODEN: EMJOD
Full Journal Title: EMBO (European Molecular Biology Organization) Journal
Language: ENGLISH
We have identified a *gene*, *fos* B, encoding a nuclear protein of 338 amino acids presenting a 70% homology with c-*fos*, whose expression is activated during G0/G1 transition. Growth factor stimulation of quiescent cells leads to a rapid and transient accumulation of *fos* B mRNA, with kinetics similar to those of c-*fos*. The induction of *fos* B mRNA levels is in part due to a dramatic increase in the transcription of the *gene*. The half-life of *fos* B mRNA is in the order of 10.sbd.15 min. Both transcriptional activation and mRNA stability are substantially increased in the presence of protein synthesis inhibitors. Immunoprecipitation studies showed that *fos* B as c-*fos* protein, forms a complex in vitro with c-*jun* and *jun* B proteins in the absence of a target binding *sequence*. Gel retardation assays demonstrated that *fos* B protein positively influences the binding of c-*jun* and *jun* B proteins to an AP-1 binding consensus *sequence*, suggesting that *fos* B protein plays a role in control of *gene* expression.
Descriptors/Keywords: NIH 3T3 CELLS *GENE* EXPRESSION AMINO ACID *SEQUENCE* NUCLEOTIDE *SEQUENCE* MOLECULAR *SEQUENCE* DATA
Concept Codes:
*02506 Cytology and Cytochemistry-Animal
*03506 Genetics and Cytogenetics-Animal
*10062 Biochemical Studies-Nucleic Acids, Purines and Pyrimidines
*10064 Biochemical Studies-Proteins, Peptides and Amino Acids
*10506 Biophysics-Molecular Properties and Macromolecules
10052 Biochemical Methods-Nucleic Acids, Purines and Pyrimidines
10054 Biochemical Methods-Proteins, Peptides and Amino Acids

6/9/78 (Item 78 from file: 5)
DIALOG(R)File 5:BIOSIS PREVIEWS(R)

7054398 BIOSIS Number: 87114919
JUN-D A THIRD MEMBER OF THE *JUN* *GENE* FAMILY
RYDER K; LANAHAN A; PEREZ-ALBUERNE E; NATHANS D
HOWARD HUGHES MED. INST. LAB., DEP. MOL. BIOL. GENETICS, JOHN HOPKINS UNIV. SCH. MED., BALTIMORE, MD. 21205.
PROC NATL ACAD SCI U S A 86 (5). 1989. 1500-1503. CODEN: PNASA
Full Journal Title: Proceedings of the National Academy of Sciences of the United States of America
Language: ENGLISH
The protooncogene c-*jun* encodes a component of the transcription factor AP-1. Both murine c-*jun* and a related *gene* (*jun*-B) are rapidly activated in BALB/c 3T3 cells by serum growth factors. We report here the cloning and anlaysis of a *CDNA* encoding a third member of the murine *jun* family, *jun*-D. The amino acid *sequence* encoded by *jun*-D has two extensive regions of homology with the other *Jun* proteins. One homology region includes the *DNA*-*binding* domain and sequences required for dimer formation and interation with the *Fos* oncoprotein; the other includes the

acidic *sequence* thought to be involved in *gene* activation. All three *jun* mRNAs are present in a variety of murine tissues and cell lines. In resting 3T3 cells, *jun*-D is expressed at a higher level compared to c-*jun* and *jun* -B, and its transcription is stimulated only slightly by serum growth factors. Thus, *jun*-D appears to be regulated differently than c-*jun* and *jun*-B.
Descriptors/Keywords: MOUSE PROTOONCOGENE TRANSCRIPTION FACTOR AP-1 *DNA* *BINDING* DOMAIN ACIDIC *SEQUENCE* MOLECULAR *SEQUENCE* DATA AMINO ACID *SEQUENCE* EMBL-J04509 GENBANK-J04509 *SEQUENCE* HOMOLOGY
Concept Codes:
*03506 Genetics and Cytogenetics-Animal
*10062 Biochemical Studies-Nucleic Acids, Purines and Pyrimidines
*10300 Replication, Transcription, Translation
*10506 Biophysics-Molecular Properties and Macromolecules
*13012 Metabolism-Proteins, Peptides and Amino Acids
*13014 Metabolism-Nucleic Acids, Purines and Pyrimidines
10010 Comparative Biochemistry, General
10064 Biochemical Studies-Proteins, Peptides and Amino Acids
Biosystematic Codes:
86375 Muridae
Super Taxa:
Animals; Chordates; Vertebrates; Nonhuman Vertebrates; Mammals; Nonhuman Mammals; Rodents

6/9/89 (Item 89 from file: 5)
DIALOG(R)File 5:BIOSIS PREVIEWS(R)

6987264 BIOSIS Number: 87047785
DNA *BINDING* ACTIVITIES OF THREE MURINE *JUN* PROTEINS STIMULATION BY *FOS*
NAKABEPPU Y; RYDER K; NATHANS D
HOWARD HUGHES MED. INST. LAB., JOHN HOPKINS UNIV. SCH. MED., BALTIMORE, MD. 21205.
CELL 55 (5). 1988. 907-916. CODEN: CELLB
Full Journal Title: Cell
Language: ENGLISH
Three members of the *Jun*/AP-1 family have been identified in mouse *cDNA* libraries: c-*Jun*, *Jun*-B, and *Jun*-D. We have compared the *DNA* *binding* properties of the *Jun* proteins by using in vitro translation products in gel retardation assays. Each protein was able to bind to the consensus AP-1 site (TGACTCA) and, with lower affinity, to related sequences, including the cyclic AMP response element TGACGTCA. The relative binding to the oligonucleotides tested was similar for the different proteins. The *Jun* proteins formed homodimers and heterodimers with other members of the family, and they were bound to the AP-1 site as dimers. When *Fos* translation product was present, *DNA* *binding* by *Jun* increased markedly, and the DNA complex contained *Fos*. The C-terminal homology region of *Jun* was sufficient for *DNA* *binding*, dimer formation, and interaction with *Fos*. Our general conclusion is that c-*Jun*, *Jun*-b, and *Jun*-D are similar in their *DNA* *binding* properties and in their interaction with *Fos* . If there are functional differences between them,they are likely to involve other activities of the *Jun* proteins.
Descriptors/Keywords: CONSENSUS NUCLEOTIDE *SEQUENCE* MOLECULAR *SEQUENCE* DATA
Concept Codes:
*03506 Genetics and Cytogenetics-Animal

*10062 Biochemical Studies-Nucleic Acids, Purines and Pyrimidines
*10064 Biochemical Studies-Proteins, Peptides and Amino Acids
*10506 Biophysics-Molecular Properties and Macromolecules
02506 Cytology and Cytochemistry-Animal
Biosystematic Codes:
86375 Muridae
Super Taxa:
Animals; Chordates; Vertebrates; Nonhuman Vertebrates; Mammals; Nonhuman Mammals; Rodents

6/9/99 (Item 99 from file: 5)
DIALOG(R)File 5:BIOSIS PREVIEWS(R)

6448653 BIOSIS Number: 85049174
HUMAN PROTO-ONCOGENE C-*JUN* ENCODES A *DNA* *BINDING* PROTEIN WITH STRUCTURAL AND FUNCTIONAL PROPERTIES OF TRANSCRIPTION FACTOR AP-1
BOHMANN D; BOS T J; ADMON A; NISHIMURA T; VOGT P K; TJIAN R
HOWARD HUGHES MED. INST., DEP. BIOCHEMISTRY, UNIV. CALIF., BERKELEY, CALIF. 94720.
SCIENCE (WASH D C) 238 (4832). 1987. 1386-1392. CODEN: SCIEA
Language: ENGLISH
Nuclear oncogene products have the potential to induce alterations in *gene* regulation leading to the genesis of cancer. The biochemical mechanisms by which nuclear oncoproteins act remain unknown. Recently, an oncogene, v-*jun*, was found to share homology with the *DNA* *binding* domain of a yeast transcription factor, GCN4. Furthermore, GCN4 and the phorbol ester-inducible enhancer binding protein, AP-1, recognize very similar DNA sequences. The human proto-oncogene c-*jun* has now been isolated, and the deduced amino acid *sequence* indicates more than 80 percent identity with v-*jun*. Expression of cloned c-*jun* in bacteria produced a protein with *sequence*-specific *DNA* *binding* properties identical to AP-1. Antibodies raised against two distinct peptides derived from v-*jun* reacted specifically with human AP-1. In addition, partial amino acid *sequence* of purified AP-1 revealed tryptic peptides in common with the c-*jun* protein. The structural and functional similarities between the c-*jun* product and the enhancer binding protein suggest that AP-1 may be encoded by c-*jun* . These findings demonstrate that the proto-oncogene product of c-*jun* interacts directly with specific target DNA sequences to regulate *gene* expression, and therefore it may now be possible to identify genes under the control of c-*jun* that affect cell growth and neoplasia.
Descriptors/Keywords: CARCINOGENESIS
Concept Codes:
*02508 Cytology and Cytochemistry-Human
*03508 Genetics and Cytogenetics-Human
*10010 Comparative Biochemistry, General
*10064 Biochemical Studies-Proteins, Peptides and Amino Acids
*10506 Biophysics-Molecular Properties and Macromolecules
*24007 Neoplasms and Neoplastic Agents-Carcinogens and Carcinogenesis
*25508 Developmental Biology-Embryology-Morphogenesis, General
10054 Biochemical Methods-Proteins, Peptides and Amino Acids
10062 Biochemical Studies-Nucleic Acids, Purines and Pyrimidines
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